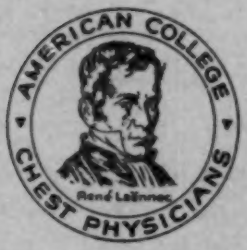
VOLUME XX NUMBER 1

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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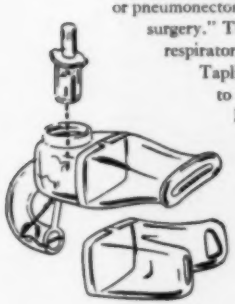

Taplin et al.[1] state that nearly all organisms infecting the respiratory tract are sensitive to either penicillin or streptomycin and that these drugs in micronized form for inhalation appear to offer definite advantages over other methods of administration. Further, "that prophylactic measures used to prevent the accumulation of bronchial secretions have materially reduced the incidence" of postoperative pneumonia. Against penicillin-susceptible organisms, the AEROHALOR plays an important role. The treatment is simple and effective—the patient simply "smokes" the AEROHALOR like a pipe. For comprehensive literature which discusses indications, dosage and clinical results, write Abbott Laboratories, North Chicago, Illinois.

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1. Taplin, G., Cohen, S., and Mahoney, E. (1948), Prevention of Postoperative Pulmonary Infections, J. Amer. Med. Assn., 138:4, Sept. 4.

2. Krasno, L., and Rhoads, P. (1949), The Inhalation of Penicillin Dust; Its Proper Role in the Management of Respiratory Infections, Amer. Prac., 1:649, July.

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VOLUME XX JULY 1951 NUMBER 1

CONTENTS:

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DISEASES *of the* CHEST

VOLUME XX JULY 1951 NUMBER 1

Tibione[1] in the Treatment of Tuberculosis Activity, Dosage and Toxic Manifestations[2]

SAMUEL H. BELGOROD, M.D.,[3] HYMAN ALEXANDER, M.D., F.C.C.P.,[4] CHARLES E. MEIDT, M.D.[5] and JOHN McGALEY, M.D.[6]
New York, New York

During the past two decades the revolutionary discoveries in the fields of antibiotics and chemotherapy have served as an added incentive in the ceaseless search for an effectual therapeutic antagonist against the inciting agent of tuberculosis. Earlier therapeutic measures such as bed rest, climatotherapy, heliotherapy, phrenicectomy, pneumothorax, and pneumoperitoneum (which is now undergoing re-evaluation by various investigators) represented attempts at healing through improved environmental conditions and enforced rest for the afflicted organs. By minimizing activity it was hoped that the disease process could be kept localized until the body was able to marshal its natural forces of resistance and immunity and eventually allay the disease process. More recent efforts have been primarily surgical as exemplified by thoracoplasty, segmental resection, lobectomy, and pneumonectomy. The long range results of the latter three meas-

[1] "TIBIONE" is the trade mark of Schenley Laboratories, Inc., which designates exclusively its brand of amithiozone. Amithiozone is the generic name (approved by the Council on Medicine and Pharmacy of the American Medical Association) of the thiosemicarbazones used in the treatment of tuberculosis and referred to in this article. The amithiozone used in this study was supplied through the courtesy of Schenley Laboratories, Inc.

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[4] Visiting Physician.

[5] Chief Resident Physician.

[6] Resident Physician.

We are deeply indebted to Drs. A. Bereczeller and G. Gold for their invaluable assistance in carrying out the tremendous amount of laboratory work essential for this investigation.

ures are still in the process of evaluation, but they do possess the one great advantage of permanent removal of diseased and destroyed tissue despite any other drawbacks.

In the realm of antibiotics, the first important step toward overcoming the ravages of the tubercle bacillus was brought about by the discovery of streptomycin by Waksman, Schatz, and Bugie, in 1944.[1] Two years later, Lehmann[2] introduced para-aminosalicylic acid, a chemotherapeutic agent which, though less potent than streptomycin, was, nevertheless, a useful addition to our armamentarium in the struggle against tuberculosis.

In 1940,[3] Domagk found that both sulfathiozole and sulfathiodiazole possessed a high degree of activity, in vitro, against the mycobacterium tuberculosis. In this discovery lay the genesis of the thiosemicarbazones which were subsequently synthesized by Behnisch, Mietzsch and Schmidt, and of which amithiozone is one.

The Germans have been using the thiosemicarbazones since 1948 and, to date, have had an opportunity to evaluate its results on several thousand patients. In 1949, Hinshaw and McDermott[5] investigated the drug in Germany and published a preliminary report on its possible utility and toxicity. Since that time the substance has been the subject of intensive research in animals and humans, primarily for its toxic effects.[6] On the basis of this work, it was concluded by many that the drug was toxic and dangerous, with the result that its use was either abandoned or not considered. It is felt that this conclusion was not at all justified since it was based on toxicity experiments in which dosages were graduated to exceedingly high levels. We feel that amithiozone, when used in proper dosage, is relatively non-toxic and may prove a valuable addition in our methods for treatment of tuberculosis.

At this juncture, it would not be amiss to recall the fact that streptomycin, in its original dosage schedules, was also considered toxic because of its potential for production of eighth cranial nerve damage. However, it has since been shown that the present lower doses are no less effective therapeutically while noxious effects have been largely eliminated.

Anti-Tuberculous Activity of Amithiozone in Vitro: The inhibitory effect of amithiozone on the tubercle bacillus is greater than that of either PAS or streptomycin. Thus, amithiozone, in dilutions of 1:300,000 will inhibit growth of M. tuberculosis grown on egg medium to which p-aminobenzoic acid has been added. Under similar circumstances, streptomycin is effective in dilutions up to 1:1,00,000, while PAS is active in dilutions of 1:5,000 or less. We have here a parallelism between the in vitro activity of a drug and the magnitude of the effectual in vivo dose. Thus, with ami-

thiozone only 0.1 to 0.15 grams daily are required; with streptomycin, 1 gram daily or 1 gram three times a week; with PAS, 12 grams daily.[8]

It is of interest to note that tuberculin ointment loses its potency when mixed with amithiozone and is allowed to stand for a time. This does not occur with streptomycin or PAS.[9] Tubercle bacilli exposed to a 1 per cent solution of streptomycin from four to eight weeks show no destruction of infective power, while such power is lost in from four to eight weeks on exposure to a 1 per cent solution of PAS. Infectiousness of the bacilli was completely destroyed in a short time when acted on by a 1 per cent solution of amithiozone dissolved in ethylene glycol. It would appear, therefore, that the mode of action of the three drugs differs.

According to the work of Domagk, Behnisch, Mietzsch, and Schmidt,[11] it is the sulfur atom of the thiosemicarbazones which plays the important role, the corresponding semicarbazones have relatively little action. From a chemical standpoint, the thiosemicarbazones bear an obvious relationship to antithyroid drugs, whereas from the physiological point of view, they are related to 17-hydroxy-11-dehydro-corticosterone. The latter may explain some of the effects of amithiozone on certain types of arthritis.

Activity of Amithiozone in Animals: In marked contrast to streptomycin, animals are able to tolerate amithiozone in far greater doses than the human species. Thus, rats or rabbits could withstand 0.5 grams per kg. for prolonged periods without ill effects, and occasionally even 1 gram per kg.[12] Compare this with the 0.10 to 0.15 grams of the drug per day for humans.

In a series of experiments conducted by Carlson, Gainer, and Feldman,[13] it was noted that animals treated with thiosemicarbazones showed markedly less grossly visible lesions than did untreated controls, and in a manner similar to that of streptomycin. Both grossly and microscopically, there was regression and healing of lesions. With a combination of amithiozone and streptomycin, there was greater and more rapid healing than when either agent was used alone.

Amithiozone Resistance: The occurrence of the phenomenon of resistance of tubercle bacilli to amithiozone has been established in this country with dosages as low as 200 mg. daily.[15] This is in contrast to the findings of the Germans who could detect no such resistance.[16] Whether the simultaneous use of amithiozone and streptomycin results in a synergism which causes mutual retardation or prevention of resistance is a matter which remains to be solved.

Clinical Investigations: In February, 1950, this study was instituted at Sea View Hospital with a dual purpose; 1) to determine

the actual toxicity of amithiozone in the dosage employed, and 2) to observe the therapeutic effectiveness of the thiosemicarbazones alone and in combination with streptomycin and/or PAS.

A review of the literature with special attention to the observation of the German investigators, who have used the drug extensively, indicates that the thiosemicarbazones do not act in accordance with the law of mass action, i.e., that the blood level of the substance does not reflect its therapeutic efficacy.[17] Whether or not there is an imponderable factor of tissue concentration of the drug remains a subject of further probing and research. The toxic effects observed in the earlier clinical trials with the thiosemicarbazones led us to conclude that the dosage was excessive. We were further impressed with the beneficial effects of the drug despite symptoms of toxicity with large doses. This inevitably brought us to the idea that if similar clinical results could be brought about with small quantities of the drug over a longer period of time, we would have at hand a valuable adjunct chemotherapeutic agent in the treatment of tuberculosis, provided that adverse effects were either minimized or eliminated.

Our first opportunity to use amithiozone occurred on November 23, 1949. The patient, a white male, 26 years of age, was admitted to the hospital in a critical condition. He had had left artificial pneumothorax and subsequently developed a bronchopleural cutaneous fistula on the same side, with a concomitant mixed infection tuberculous empyema. The contralateral lung was the seat of extensive cavitary disease in the upper lobe, with a marked bronchogenic dissemination through the remainder of the right lung field. He was cachectic, markedly dyspneic, and with septic temperatures reaching 103 degrees F. by mouth. His weight was 76 pounds. The hemogram was Hg. 11.5 grams, RBC 4,010,000, WBC 13,750 with a normal differential count. Liver function studies and urinalyses were normal. The patient had never had any antibiotic or chemotherapy.

In view of his critical condition, treatment was instituted at once with streptomycin, 1 gram daily; PAS, 4 grams t.i.d., and amithiozone, 100 mg. t.i.d. orally. The dosage of 300 mg. of amithiozone daily was decided upon because of the experience of Heilmeyer[18] who found that administration of the drug in dosage of 100 to 300 mg. daily yielded maximum therapeutic effects with a minimal toxicity. The seriousness of the patient's condition warranted what we considered the largest dose of the substance consistent with safety and tolerance.

On November 30, 1949, because of nausea and vomiting, PAS was discontinued arbitrarily, and the gastro-intestinal disturbances promptly subsided. Thereafter, only amithiozone and streptomycin

were administered. On December 15, 1949, three weeks after the inception of therapy, the patient suddenly became moderately cyanotic and more markedly dyspneic. A blood count at this time disclosed the following:

Hemoglobin	9 grams
Red Blood Cells	3,400,000
White Blood Cells	1,620
Polymorphonuclears	9 per cent
Stab Forms	0 per cent
Lymphocytes	88 per cent
Monocytes	1 per cent
Eosinophiles	1 per cent
Basophiles	1 per cent

Amithiozone was stopped at once, and streptomycin was continued. The patient was given transfusions of 500 cc. of blood every three days until he had had a total of 2000 cc. In addition, 600,000 units of depot penicillin were administered daily intramuscularly. It was interesting to note that tests of hepatic function at this time indicated no disturbance in the liver. On this regimen, a blood count taken on December 19, 1950, was:

Hemoglobin	13.5 grams
Red Blood Cells	4,830,000
White Blood Cells	3,500
Polymorphonuclears	26 per cent
Stab Forms	10 per cent
Lymphocytes	48 per cent
Monocytes	6 per cent
Eosinophiles	9 per cent
Basophiles	1 per cent

By December 27, 1949, the hemogram showed further improvement:

Hemoglobin	16.5 grams
Red Blood Cells	5,390,000
White Blood Cells	15,600
Polymorphonuclears	66 per cent
Stab Forms	15 per cent
Lymphocytes	16 per cent
Monocytes	3 per cent

Thus, within a period of 12 days after amithiozone was discontinued and intensive measures for restitution of the blood level instituted, the anemia, leucopenia, and granulocytopenia had been corrected.

Following this episode, it was determined that a more conservative routine in the administration of amithiozone was essential. Hence, with slight modification, the plan of Hohenner and Linke[19] was used as a basis for dosage. The schedule consisted of 50 mg. q.d. for seven to 10 days, then 50 mg. b.d. (100 mg. daily) for

seven to 10 days, and finally 50 mg. t.i.d. (150 mg. daily) indefinitely. On January 1, 1950, this patient was started on the new routine and has been taking 150 mg. of amithiozone daily since that time without ill effect.

In February of 1950, a group of 84 patients was selected for determination of toxic and therapeutic effects of amithiozone alone, in the dosage of 150 mg. daily as outlined above, and of amithiozone in combination with streptomycin and/or PAS. The group consisted of 42 females and an equal number of males. The great majority of the patients had far advanced bilateral cavitary disease and the remainder had moderately advanced lesions according to the N.T.A. classification. There were no instances of minimal disease. Detailed analysis of extent of disease will be described in a future communication on the therapeutic effects of amithiozone.

For purposes of comparative study of therapy, the cases were divided into four groups of about 20 patients each. Group one received amithiozone alone; group two, amithiozone and PAS; group three, amithiozone and streptomycin; group four, amithiozone, streptomycin and PAS. Streptomycin dosage was 1 gram daily intramuscularly, PAS was given orally in divided doses of 4 grams t.i.d. or a total of 12 grams daily. Amithiozone was also given orally in divided doses of 50 mg. t.i.d. or a total of 150 mg. daily. All patients given streptomycin were carefully screened to ascertain that they had not had any therapy previously with this antibiotic. Similarly, any cases which might be suitable for surgical measures were eliminated from the series.

At the time of writing this article (early December, 1950) our clinical investigation is comprised of a group of 75 patients who have been on therapy for from six to 10 months. The vast majority have been on one or another of the four medication schedules for nine or 10 months. Four of the patients have died, others have signed out of the hospital or have been transferred to different wards. Hence, though 84 cases have at all times been under observation, it was deemed best to choose only those who had been on treatment for six months or longer.

Laboratory Procedures: The following laboratory routines were performed for all patients:

1) A complete blood count twice weekly for an interval of five months following which hemograms were done once a month.

2) Sedimentation rates every two weeks for three months, then once a month.

3) Total serum protein determinations with albumin-globulin ratio every two weeks for three months, then once a month.

4) Cephalin flocculation tests every two weeks for three months, then once a month.

5) Bromsulphalein tests once a month for the first two months of the study.

6) Urinalyses once a month throughout the period of investigation.

A base line for each case was established by carrying out all the laboratory routines before embarking on any type of treatment. Subsequently, the tests were done at the intervals indicated above.

Studies of Toxicity and Side Reactions—Laboratory Results:

1) Blood Counts.

A) Hemoglobin and Red Blood Cells: Since hemograms were done twice a week, a fall in hemoglobin or red blood cells was considered significant only if it was sustained for a period of one or more weeks and then followed by a gradual increase to or above the original level.

On this basis, a total of 32 patients (43 per cent) suffered a drop in hemoglobin averaging 1.5 grams, with the greatest fluctuation from 0.5 to 3.5 grams. The fall of red blood cells varied from 500,000 to 1,000,000 per cubic mm. of blood. The decrease in both components began, on an average, between the fourth and eighth weeks after the inception of therapy. Spontaneous restitution then followed and was usually complete within a matter of two to four weeks. The earliest instance of a fall in red cells and hemoglobin was on the fourth day after amithiozone was started, while the longest period required for an increase to the original level was 12 weeks after the time of greatest depression of the blood elements under discussion.

Table I gives the analysis under the various therapeutic groupings, of decrease in hemoglobin and red blood cells.

Hence, 13 males (31 per cent of the male group) and 19 females (50 per cent of the female group) were affected. This does not include the patient previously described who had a hematologic crisis with 300 mg. of amithiozone daily. In none of the above cases were transfusions or hematinics required. The increase in hemoglobin and red blood cells occurred spontaneously, and in many

TABLE I

Fall in Hgb. and RBC	T*	TP*	TS*	TSP	Total
Male	3	3	2	5	13
Female	4	3	5	7	19
Total	7	6	7	12	32

T = Tibione P = PAS S = Streptomycin

instances exceeded the original levels. In the remaining cases these blood elements showed either an increase or remained unchanged. It is of interest to note that the greatest number of patients affected occurred in the group receiving all three medications.

B) White Blood Cells: The alterations in leucocytes were more marked than with the blood elements above described. Sixty patients (80 per cent) showed a drop in white cells and of these, 34 were males (80 per cent of the male group) and 26 were females (79 per cent of the female group). Depression of the white count generally occurred from the first to the fourth weeks after amithiozone was started, and though the decline might be continuous, it was more likely to be fluctuant with a definite downward trend. The point of greatest fall of the white blood cells took place at any time from one to several months subsequent to the institution of therapy. Here, too, a spontaneous increase then became apparent.

The determination of a significant decrease in white blood cells was entirely dependent upon the levels of counts before and after amithiozone was started. Thus a fall from 16,000 to 12,000 WBC/cu. mm. would be of far less import than a drop from 5,000 to 3,000 WBC/cu. mm. Consequently, each patient's individual series of leucocyte counts was necessarily considered separately.

There was a total of 15 cases (20 per cent) in which the white cells gradually fell to between 4,000 and 5,000 per cu. mm. and in one of these continued to drop to 3,650. The base line counts varied from 4,700 to 23,000. In all of these instances, increases subsequently occurred without the necessity for any special measures, and there have been no recurrences of drop in white blood cells.

As with the leucocytes, a diminution in granulocytes was noted in 35 patients (47 per cent). In 25 instances, the polymorphonuclears fell to between 40 and 50 per cent, while in 10 others it was depressed to between 30 and 40 per cent, the lowest recording having been 33 per cent. Again, there followed rapid, spontaneous increases which have since been sustained. Table II indicates the breakdown of the drop in polymorphonuclear cells in these patients.

Though there was an over-all parallelism between the total white cell count depression and fall in polymorphonuclears, the

TABLE II

Fall in Polymorphonuclear cells	To 40-50 per cent	To 30-40 per cent	Total
Male	14	2	16
Female	11	8	19
Total	25	10	35

point of greatest depression of the one did not necessarily coincide with that of the other.

Eosinophilia is a well known and common concomitant of treatment with streptomycin. PAS is not known to produce any such effect when used by itself. Table III graphically illustrates the findings.

TABLE III

Per cent Eosinophiles	T*	TP*	TS*	TSP	Total
5 to 9 per cent	13	13	13	14	53
10 per cent and over	2	3	4	6	15
Total	15	16	17	20	68

T = Tibione P = PAS S = Streptomycin

A total of 68 patients developed some degree of eosinophilia and of these 31 or a little less than half received no streptomycin. In 15 cases the rise in eosinophiles at some time during the course of observation was 10 per cent or over. Five of these patients received no streptomycin. Thus, a rise in eosinophiles was slightly more prevalent and more intense in those instances where antibiotic therapy was employed.

The eosinophilia was generally transitory and might occur at any time during the period of therapy, but was most likely to be encountered during the first three months and with possible repetitions at later dates.

C) Sedimentation Rates: The sedimentation rate displayed a peculiar behavior. Though it tended to fall, in most instances, during the first one to two months of therapy, it then rose irregularly and was completely unpredictable irrespective of whether amithiozone was employed alone or in conjunction with the other medicaments. Indeed, the sedimentation rates completely failed to conform with improvement or progression of the disease. Hence, this procedure is not utilizable as a prognostic sign when the thiosemicarbazones are employed. These findings are in accordance with those of Delfs and others.[20]

D) Liver Function Tests: (I) Serum Proteins, Total: If the normal value for total serum proteins is accepted as 7.2 grams/100 cc. of blood ± 0.35,[21] then normal levels prior to the therapy were found in only seven (9 per cent) of our patients, while in one (0.75 per cent) it was moderately lowered (5.6 grams/100 cc. of blood). In the remaining 67 cases the base line levels of total serum proteins varied between 8.0 and 11.2 grams/100 cc. with an average of 8.96 grams/100 cc.

Within two to six weeks after onset of therapy those values which were normal or below rose to 8.0 grams/100 cc. or more, and were generally maintained at the higher levels. Of the 67 patients whose original total serum proteins were elevated, no definite pattern could be discerned. Occasionally, the values would dip to normal irregularly but would soon increase again.

(II) Albumin-Globulin Ratio: The vast majority of the patients, before and during therapy, showed an increase in globulin, including those who had a normal total serum protein, so that there was a distinct tendency toward equalization or slight reversal of the albumin-globulin ratio. It was this globulin elevation which was responsible for the overall total protein rise. During the course of treatment, no definite trend in reversal or correction of the ratio was apparent with improvement or progression of the disease.

(III) Cephalin Flocculation Test: Pre-treatment tests disclosed the breakdown of 48 hour results shown in Table IV. Thus, six (8 per cent) of the patients showed a 2+ flocculation after 48

TABLE IV
CEPHALIN FLOCCULATION TEST

Reading at end of 48 hrs.	O	VFT-T	1 plus	2 plus	3 plus
Male	19	12	7	2	2
Female	15	8	5	4	1
Total	34	20	12	6	3

hours, while three (4 per cent) revealed a 3+. In each of these instances, after therapy was started, the 48 hour flocculation became a trace or less within two to four weeks. Subsequently, the results for all patients were variable with erratic rises and falls. At times the increase was up to 2+ after 48 hours, and in very occasional instances 3+ as is evident from Table V. When the 48 hour result rose to 3+ the test was repeated within two to five days and if the rise was sustained, amithiozone was discontinued. Thus, two females and one male developed a 3+ flocculation tests after four, five, and nine months respectively, along with moderate

TABLE V
CEPHALIN FLOCCULATION TEST

Reading at end of 48 hrs.	2 plus	3 plus
Male	5	2
Female	8	2
Total	13	4

degrees of icterus. In association with this there was slight to moderate hepatomegaly and anorexia. Upon cessation of amithiozone the jaundice disappeared within four to six weeks, as did the hepatomegaly and anorexia. The two females have again been given amithiozone while the male will again be given the drug within two or three weeks. The maximum dosage in each of these cases will be maintained at 100 mg. daily.

The fourth patient who had a flocculation of 3+ at 48 hours had no other signs of liver damage and his subsequent tests showed a prompt fall to 1+ and then to 0, so that there was no necessity for discontinuance of amithiozone. It is of interest to note that one of our male patients with Laennec's cirrhosis has been on thiosemicarbazones for nine months without any evidence of further liver damage or hepatic insufficiency.

E) Urinary System: Routine urinalyses disclosed no significant changes throughout the period of investigation.

Clinical Observations.

A) Gastro-Intestinal System: Symptoms in this category were classified as mild and moderate to severe. Mild manifestations consisted of anorexia and nausea. Moderate to severe symptoms included vomiting and diarrhea as well as nausea and anorexia. These were most likely to become evident from the third to sixth week of treatment. Table VI discloses the incidence and severity of gastro-intestinal disturbances.

It was found that administration of an anti-spasmodic such as belladonna or one of the belladonna-like alkaloids would often alleviate gastro-intestinal distress and make unnecessary any discontinuation of amithiozone. However, in six cases (8 per cent) the drug had to be stopped because of severe symptoms. After 10 to 14 days medication was resumed starting with a dose of 25 mg. daily and gradually building up to 150 mg. daily. In two of these patients it was necessary to halt therapy once more and then start over again. Since then, the drug appears to have been well tolerated. The remaining two patients refused further treatment.

B) Skin Rashes: One patient, a female, developed generalized

TABLE VI
GASTRO INTESTINAL SYMPTOMS

Symptoms	Mild	Moderate to severe	Total
Male	8	6	14
Female	7	5	12
Total	15	11	26

urticarial and papular eruption. She had been taking PAS and amithiozone and both drugs were stopped. The rash subsided within two weeks. Two weeks later she was again given amithiozone and several days thereafter the lesions reappeared. Once more the drug was discontinued and when the rash had disappeared PAS was started. After one month there were no untoward effects and no reappearance of the skin eruption. Hence, PAS was interrupted and the patient once more was given amithiozone in doses of 25 mg. daily. The rash became evident within a few days, whereupon amithiozone was completely discontinued since it was obvious that this was a case of amithiozone sensitivity.

C) Conjunctivitis: This was not encountered in our series although its occurrence as an isolated phenomenon is reported by the Germans.[22]

D) Central Nervous System: None of the patients in this investigation developed any signs or symptoms of central nervous system damage or irritation although such cases have been reported in the German literature.[23]

E) Miscellaneous: Many varieties of symptoms have been recorded in toxicity tests. These include headache, occular disturbances, malaise, drowsiness, hyperesthesias, etc. None of these was noted in any of our cases.

Comment

It is our considered opinion that amithiozone, when administered in proper dosage and under competent medical supervision, is a relatively safe drug and may prove of considerable value as an anti-tuberculous agent. Since November 1, 1950, we have reduced the daily dose to 50 mg. b.i.d. (100 mg. q.d.) in an effort to determine whether the lesser quantity will lead to further elimination of adverse effects without diminution in therapeutic potency. These results will be reported at a later date.

On a dose of 150 mg. somewhat less than half of our patients displayed a mild to moderate fall in hemoglobin and red blood cell count. In practically all of our cases there resulted varying degrees of depression of the leucocytes and in only 20 per cent was there a drop to a level of 4,000 to 5,000 per cu. mm. of blood. In all these cases, however, there were spontaneous increases to higher levels which were subsequently maintained without the necessity for special measures. The changes in the blood elements are not at all surprising in view of the fact that amithiozone is chemically related to the antithyroid drugs. Apparently the granulopenia occurs for similar reasons. Though there were 10 instances of polymorphonuclear counts of from 30 to 40 per cent, these were of short duration. It is well to bear in mind, however, that in any chronic

wasting disease such as chronic pulmonary tuberculosis the demands upon the blood forming organs are excessive, and fatigue of the latter is apt to manifest itself as a granulocytopenia or a relative leucopenia. Pretreatment hemograms in four patients revealed white counts varying from 4700 to 5300/cu. mm. of blood and with polymorphonuclear counts from 43 to 51 per cent. In four other cases the base line polymorphonuclear cell determination varied between 30 and 40 per cent, the lowest being 34 per cent, with total WBC/cu. mm. 8,000 or more. In all these instances the counts became normal within two months after treatment was started.

It would appear, therefore, that with the dosage schedule employed any hematologic disturbances based on the action of amithiozone are transitory and reversible, and do not require any halt in therapy unless there should be changes more profound than those which we have observed.

The significance of the eosinophilia is a controversial subject. If it should represent a tissue hypersensitivity then there are a number of factors, including the drugs, which may act as possible inciting agents. Certainly, the problem is beyond the scope of this paper. All that may be said is that amithiozone does produce a transitory eosinophilia, the latter becoming more pronounced when streptomycin is added.

Pre-treatment total serum proteins and albumin and globulin determinations were of interest because of the manifest hyperproteinemia and hyperglobulinemia seen in these patients with long standing disease. Of added note was the elevation in total serum proteins of those patients whose original determinations were normal or below. The increase was brought about primarily through a rise in the globulin. As previously stated, the remaining cases subsequently evinced no marked deviations from base line levels. In this connection electrophoresis of the plasma of tuberculous patients was carried out by Heilmeyer[24] and Klee[25] independently. They both found that under thiosemicarbazone therapy there was a diminution of alpha globulins with a marked increase in gamma globulins which would account for the elevation in total globulins and hence, total serum proteins. How this effect is produced is unknown.

The cephalin flocculation tests revealed that a small number of tuberculous patients will show a 2+ result after 48 hours while a still lesser number will have a 3+ result. This appears to be no contraindication of amithiozone therapy in the absence of any other signs of liver damage, since these tests may very well be reversed under treatment. If during medication a 3+ should develop and persist on one or two repeated determinations within

the course of several days then the drug should be stopped until the test is normal again. One and two months ago, two of our patients who developed jaundice were started on amithiozone again after all signs of liver insufficiency had disappeared. There have been no recurrences of hepatic disturbances.

According to Davis, Netzer, et al.[26] amithiozone has a cumulative action but does have a definite renal threshold level. It is the latter mechanism which, therefore, makes possible administration of the drug over prolonged periods of time as in this study. Blood level determinations were not made in the course of this investigation.

Although we are not yet prepared to make any definite statement on the therapeutic efficacy of amithiozone alone or in conjunction with streptomycin and/or PAS certain features stand out and merit mention in a general fashion. Over a period of several months the fever gradually declines and remains flat unless there is renewed activity of the tuberculous process or some intercurrent infection. Cough and expectoration are markedly diminished. There is an increase in the sense of well being which brings with it improved appetite and a gain in strength. The majority of the patients showed a gain in weight, though some remained stationary and a few actually lost weight. Many of the patients have had conversion of sputa and negative gastrics for from three to seven months. Of special interest was a small group with open cavities and persistently negative sputa and gastric lavage. We are anxious to see how long this situation will obtain. Another noteworthy finding has been the extremely small number of spreads of disease in types of cases where one would expect them with greater frequency. From our studies to date it would appear that the combinations of amithiozone and streptomycin or amithiozone, streptomycin and PAS are more effective than any of these agents used by itself.

There were four deaths in this series:

1) Male—Far advanced, bilateral pulmonary disease with gastro intestinal tuberculosis and amyloidosis.
2) Female—Pulmonary insufficiency. She had had a thoracoplasty with an underlying patent cavity on one side with extensive cavitary disease in the contralateral lung.
3) Female—Rheumatic heart disease with cardiac failure.
4) Female—Fatal hemorrhage due to erosion of a large calcified tracheobronchial node into a pulmonary artery.

SUMMARY

1) This study comprises a group of 75 patients with moderately and far advanced pulmonary tuberculosis treated with amithio-

zone or with amithiozone and streptomycin and/or PAS for periods varying from six to 10 months.

2) Amithiozone shows marked anti-tuberculous activity in vitro and in animals.

3) A hematologic crisis is described in a patient who received 300 mg. of amithiozone daily, but whose blood was unaffected on a dosage of 150 mg. daily for a period of 11 months.

4) In daily dosage of 150 mg. or less, amithiozone is a safe drug when administered under medical supervision and with adequate laboratory facilities.

5) In daily dosage of 150 mg., amithiozone may be administered for prolonged periods of time.

6) In daily dosage of 150 mg., amithiozone may cause depression of any or all of the formed elements of the blood, but these alterations are transitory and restitution occurs with continued medication.

7) In daily dosage of 150 mg., amithiozone may cause a transient eosinophilia.

8) These studies do not indicate any specific effect of amithiozone on the sedimentation rate with relation to regression or progression of the disease.

9) Chronic pulmonary tuberculosis appears to be a disease characterized by hyperproteinemia and hyperglobulinemia.

10) Amithiozone heightens or maintains the hyperproteinemia and hyperglobulinemia.

11) Cephalin flocculation tests of 2+ and 3+, after 48 hours, are not rare under amithiozone therapy and may be reversible with continued medication.

12) Amithiozone may occasionally be responsible for hepatic insufficiency, jaundice, and hepatomegaly, but this reaction is reversible, and the drug may be resumed when the condition has subsided.

13) Amithiozone may cause gastrointestinal disturbances of mild to severe intensity which disappear on cessation of medication and which are less likely to recur when the drug is resumed.

14) In daily dosage of 150 mg. per centage amithiozone, conversion of sputum, and clinical improvement was noted. This will be evaluated and reported later.

15) Combinations of amithiozone with streptomycin and of amithiozone, streptomycin and PAS seem to show greater clinical promise than any one of these substances used alone, but the results are still to be determined.

RESUMEN

1) Este estudio incluye 75 enfermos con tuberculosis pulmonar moderada y muy avanzada, tratados con amithiozone o con amithiozone y estreptomicina y/o PAS por periodos de 6 a 10 meses.

2) Amithiozone muestra marcada actividad antituberculosa in vivo y en animales.

3) Se describe una crisis hematológica en un enfermo que recibió 300 mg. de amithiozone por día, pero cuya sangre no se alteró con la dosis de 150 mg. por 11 meses.

4) A la dosis de 150 mg. o menos el amithiozone es una droga segura cuando se administra bajo supervisión médica y con exámenes de laboratorio al alcance.

5) A la dosis diaria de 150 mg. el amithiozone puede ser administrado por prolongados periodos.

6) A esa misma dosis amithiozone puede causar depresión de cualquiera de los elementos sanguíneos, pero estas alteraciones son transitorias y al continuar la medicación esas alteraciones desaparecen.

7) A la dosis de 150 mg. el amithiozone puede causar una eosinofilia transitoria.

8) Estos estudios no han mostrado una acción especial sobre la sedimentación globular causada por el amithiozone en relación alguna con la mejoría o agravación de la enfermedad.

9) La tuberculosis pulmonar crónica parece una enfermedad caracterizada por hiperproteinemia e hiperglobulinemia.

10) El amithiozone eleva y mantiene la hiperproteinemia y la hiperglobulinemia.

11) No son raras las pruebas de Cefalin floculación de más dos y más tres después de 48 horas de tratamiento con amithiozone, pero pueden ser reversibles al continuarse el tratamiento.

12) El amithiozone puede ser responsable de la aparición de insuficiencia hepática, ictericia y hepatomegalia, pero esta reacción es reversible y la droga puede volverse a usar cuando la alteración ha desaparecido.

13) El amithiozone puede causar trastornos gastrointestinales de mediana o severa intensidad, que desaparecen al suspender la medicación y que ocurren con menos frecuencia cuando la droga se vuelve a usar.

14) A la dosis de 150 mg. el porcentaje de conversión del esputo y la mejoría clínica se notaron. Esto será evaluado en otra comunicación.

15) Las combinaciones de amithiozone y estreptomicina y de ambas con PAS prometen mucho, pero aún no es tiempo de evaluar los resultados.

RESUME

1) Cette étude s'applique à un groupe de 75 malades atteints de tuberculose pulmonaire à un stade modéré ou très avancé de son évolution. Ces malades ont été traités par le amithiozone, ou par le amithiozone associé à la streptomycine, ou au P.A.S., pendant des laps de temps variant de six à dix mois.

2) Le amithiozone montre une action antituberculeuse certaine in vivo et chez l'animal.

3) Les auteurs décrivent des troubles sanguins chez un malade qui avait été traité par une dose de 300 mmgr. par jour. Il n'y avait eu chez ce malade aucune perturbation de sa formule sanguine tant qu'il n'avait reçu que 150 mmgr. par jour, ce qui avait eu lieu pendant une période de onze mois.

4) Quand il s'agit de doses de 150 mmgr. par jour, ou de doses inférieures, le amithiozone est un traitement sans danger, quand il est administré sous contrôle médical et avec les recherches de laboratoires nécessaires.

5) A la dose de 150 mmgr. par jour, le amithiozone peut être prescrit pendant un temps prolongé.

6) A la dose de 150 mmgr. par jour, le amithiozone peut être cause d'une chute de certains ou de la totalité des éléments du sang, mais ces altérations sont transitoires et le retour se fait à la normale lorsque le traitement est continué.

7) A la dose de 150 mmgr. par jour, le amithiozone peut être à l'origine d'une éosinophilie transitoire.

8) Ces études ne donnent pas la preuve que le amithiozone a une action particulière sur le taux de la sédimentation.

9) La tuberculose pulmonaire chronique semble être une affection caractérisée par une hyperprotéinémie, et une hyperglobulinémie.

10) Le amithiozone élève ou maintient le taux le taux de l'hyperprotéinémie et de l'hyperglobulinémie.

11) Les tests de floculation à la "céphaline" élevés de deux ou trois degrés après 48 heures, ne sont pas exceptionnels sous l'influence du traitement par le amithiozone. Il peut y avoir retour à la normale lorsque le traitement est continué.

12) Dans certains cas, le amithiozone peut être à l'origine d'insuffisance hépatique, ictère, hépatomégalie, mais ces troubles peuvent disparaitre et l'on peut reprendre le traitement lorsque la guèrison est survenue.

13) Le amithiozone peut être à l'origine de troubles gastro-intestinaux, d'intensité variable, qui disparaissent lorsqu'on cesse le traitement.

14) A la dose de 150 mmgr., on note des modifications de l'expec-

toration et une amélioration clinique. Ceci sera l'occasion d'un travail ultérieur.

15) Les combinaisons de amithiozone avec la streptomycine, ou de amithiozone, streptomycine et P.A.S. semblent donner de meilleurs espoirs cliniques que l'une quelconque de ces substances utilisée seule, mais il est encore trop tôt pour juger des désultats.

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New Antibiotics in the Treatment of Tuberculosis*

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While para-amino salicylic acid and streptomycin have definitely established themselves in the treatment of tuberculosis, search for additional drugs for the treatment of this disease is necessitated by two facts: (1) these two compounds do not cure tuberculosis, and (2) many strains of the tubercle bacillus are or become resistant to streptomycin during treatment.

In the last few years, we have had the opportunity to examine a number of antibiotics which, supposedly, act against tubercle bacilli. Preliminary communications with notes on the experimental technic have been made.[1,2] This paper is a short summary of in vitro and animal tests, as well as a compilation of the clinical results.

Dihydrostreptomycin is somewhat superior to streptomycin in that it causes fewer side effects. However, tubercle bacilli develop resistance to dihydrostreptomycin just as they do to streptomycin. Furthermore, streptomycin-resistant organisms are not sensitive to dihydrostreptomycin. These facts necessarily limit the use of this drug.

Myomycin is inactivated by blood serum and is decomposed even at refrigerator temperature (0 to 4 degrees C.). Obviously, Myomycin is, therefore, of little value.

Viomycin inhibits tubercle bacilli in vitro in concentrations of 2 to 10 micrograms per cc., but large amounts—approximately 0.5 gram per kilogram of animal weight—are required to check experimental tuberculosis. The liver is the site of concentration of this drug. Adverse effects upon this organ may follow employment of large dosages of viomycin.

Enniatin gave favorable results in vitro, using 5 to 20 micro-

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†Deceased.

grams per cc. test medium, and employing 4 milligrams per kilogram animal weight in vivo. In its present form, however, enniatin is extremely irritating and cannot be used in man.

Chloromycetin proved to be active against certain human strains of tubercle bacilli. This effect, however, was not constant in that the in vitro and in vivo responses of the same strain often differed.

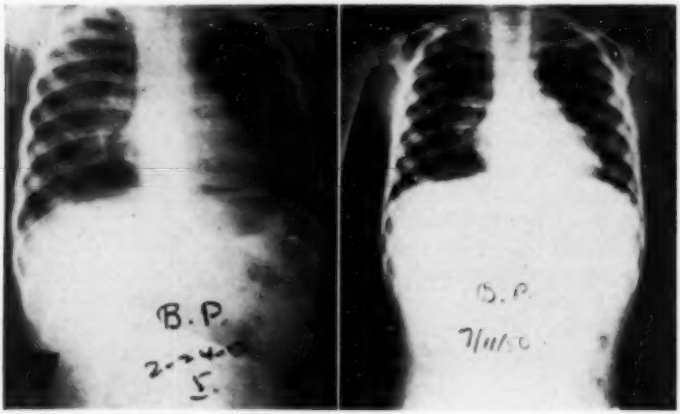

FIGURE 1 FIGURE 2

Figure 1: Tuberculous hilitis and perihilar infiltration.—*Figure 2:* Same, 4½ months later, after 62 days of neomycin treatment, showing improvement.

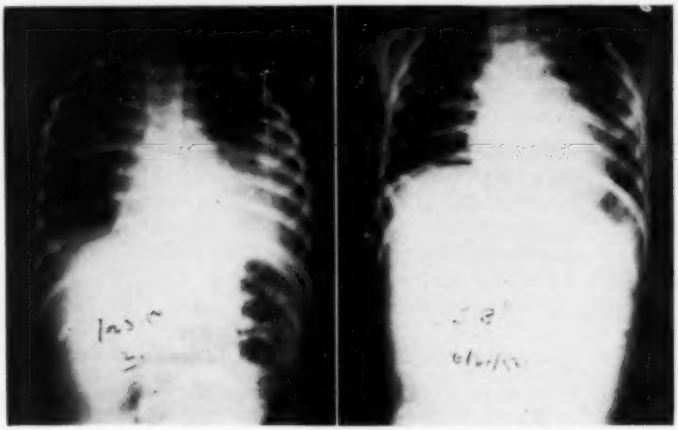

FIGURE 3 FIGURE 4

Figure 3: Bilateral tuberculous exudative pleuritis with infiltration of the middle lobe of the right lung.—*Figure 4:* Same, 5 months later, after 60 days of neomycin treatment, showing improvement.

Neomycin, an antibiotic derived from Actinomyces fradii, was effective against both streptomycin-sensitive and streptomycin-resistant tubercle bacilli. In vitro, 0.01 to 5 units were necessary to inhibit the growth of these organisms, while in animal experiments 1,000 to 10,000 units per kilogram animal weight per day gave good results in more than 90 per cent of the test animals.

In man, neomycin was well tolerated in doses up to 1,000 units per kilogram per day divided into three to four equal parts and injected intramuscularly.[3] Oral absorption was poor; therefore, the drug had to be given parenterally. Untoward effects occurred in three patients out of 127 who received neomycin. Impairment of hearing developed in two and kidney irritation in the third. The results of the use of neomycin in some conditions are in print.[4] This summary is a report only on the outcome of neomycin medication in tuberculosis.

For therapeutic experiments with neomycin in human tuberculosis, 20 patients of the Cook County Hospital were selected. Eight of these had extrapulmonary tuberculosis (one kidney, two bone and joint and five lymphoglandular forms), eight suffered from far advanced pulmonary tuberculosis, one from tuberculous meningitis, and three from combined pulmonary and extrapulmonary tuberculosis. The average dose of neomycin was 400 units per kilogram weight four times a day over a two month period.

Probably due to the fact that most of the patients were children, no untoward effects were observed, since children and young

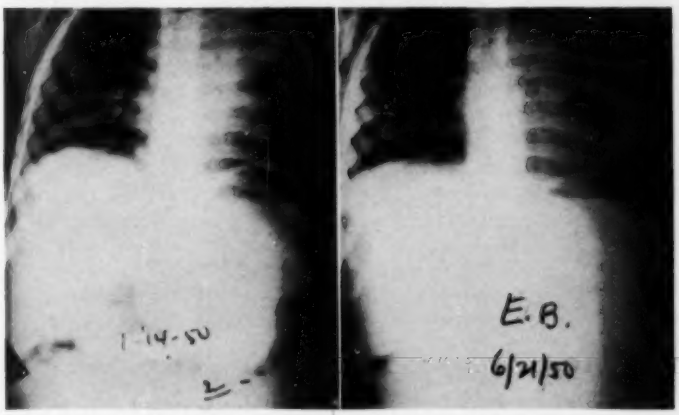

FIGURE 5 FIGURE 6

Figure 5: Tuberculous hilitis and perihilar infiltration with atelectosis of the upper lobe.—*Figure 6:* Same, 5 months later, after 35 days of neomycin treatment, showing disappearance of atelectosis and improvement of hilar adenitis.

adults are less prone to develop acoustic disturbances than older people.

Of those suffering from extrapulmonary tuberculosis, clinical manifestations disappeared in three afflicted with glandular involvement and one with tuberculosis of the sternum, while one with knee joint tuberculosis and three with tuberculous adenitis greatly improved. Of this group of eight, four had been unsuccessfully treated with streptomycin several months before the neomycin treatment was established.

In the group of 12 suffering from lung tuberculosis alone or from combined pulmonary and extrapulmonary forms, two contracted chickenpox during treatment, developed tuberculous meningitis and expired. One who came to the hospital with tuberculous meningitis also died. Two others developed tuberculous meningitis during neomycin treatment, one of them after chickenpox, but both improved later on Promizole and streptomycin therapy which was substituted for neomycin. Only two showed considerable improvement in the entire group of 12 persons afflicted with lung tuberculosis. Moderate improvement was noticed in the remaining five cases, of which one had also tuberculosis of the coxa and two had also tuberculous adenitis. Thus, seven out of the 12 pulmonary and combined cases showed varying degrees of improvement with neomycin in spite of the fact that three of them had previously demonstrated poor response to

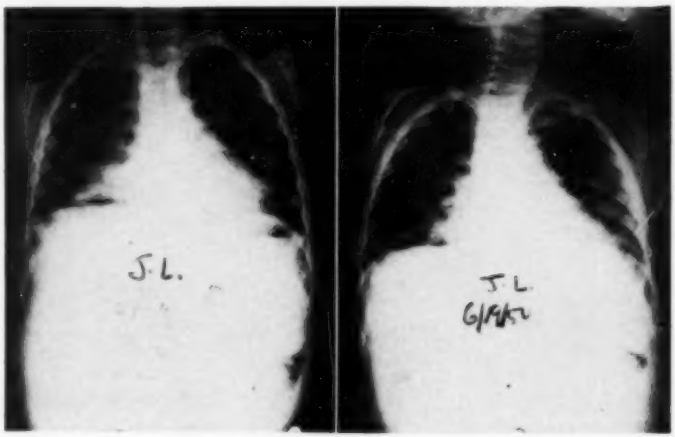

FIGURE 7 FIGURE 8

Figure 7: Tuberculous infiltrate to the right cardiophrenic angle.
Figure 8: Same, 4 months later, after 93 days of neomycin treatment, showing improvement.

streptomycin. Figures 1 to 8 show the effect of neomycin treatment on the rentgenologic picture in four cases. The pictures are self-explanatory.

The overall effect is, however, not too favorable in the group with pulmonary tuberculosis. Without doubt, such a series of cases, representing advanced tuberculous lesions, with an aggravating outbreak of chickenpox during the course of treatment will necessarily influence any attempt at evaluation of the therapeutic efficacy of neomycin. But the fact remains clear that while neomycin produces excellent results in extrapulmonary tuberculosis, it is by no means a satisfactory antituberculotic agent as far as pulmonary forms are considered.

Streptomycin-neomycin combinations are now being tested. It is hoped that such a combination may reduce the occurrence of streptomycin-resistant strains of tubercle bacilli. Blood levels achieved with this combination are very satisfactory. Reduction of the individual drug doses far below the toxic levels is made possible. This combination, however, was ineffective in 4 cases of tuberculous meningitis.

SUMMARY

Neomycin was shown to be an effective drug in extrapulmonary tuberculosis but proved considerably less favorable in advanced pulmonary forms; it was apparently without effect in tuberculous meningitis.

RESUMEN

La neomicina ha demostrado ser una droga efectiva en la tuberculosis extrapulmonar pero parece mucho menos favorable en las formas avanzadas de la tuberculosis pulmonar. Aparentemente no es efectiva en la meningitis tuberculosa.

RESUME

Les auteurs montrent que la néomycine est un produit efficace dans les tuberculoses extra-pulmonaires, mais qu'elle se montre beaucoup moins favorable dans la tuberculose pulmonaire confirmée. Elle n'a apparemment aucune action dans les méningites tuberculeuses.

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Suggestions for the Diagnostic Study of a Patient with an Abnormal X-Ray Shadow of the Chest*

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Mass x-ray surveys have increased the number of patients consulting physicians about chest diseases. In these survey films, as well as in other chest films taken routinely, abnormal shadows may be found. The roentgenologist reports these shadows as he sees them and he then interprets the findings in the light of his past experience. It must be emphasized that the roentgenologist is not able to give either a bacteriological or histological diagnosis from the x-ray film. He can, however, give accurate diagnoses in many of the films that he reads. The absolute diagnosis, however, still remains the responsibility of the clinician. The following suggestions are made to aid the physician in making diagnoses of chest lesions. It is apparent that these suggestions are minimal in character and that the physician may and can add to them.

1. What constitutes the clinical history in a case of chest disease? The history should be detailed and in the patient's own words. In addition, leading questions should bring out in particular:

a) What diseases are endemic in the patient's locality?

Case 1a: A white male, age 40 years entered the hospital in December 1938 because of a sudden pulmonary hemorrhage. The x-ray of the chest on admission to the hospital revealed an infiltration of both upper lobes. Diagnosis on admission was probable pulmonary tuberculosis. At the time of his entrance into the hospital there was a local epidemic of upper respiratory infections. The diagnostic survey did not establish the existence of pulmonary tuberculosis. The pulmonary infiltrates had disappeared by January 18, 1939, and the patient's routine yearly chest x-ray films have continued to remain normal. This case illustrates well the potential mimicry of atypical pneumonia as well as the need to know what pulmonary diseases are epidemic in the patient's environment.

b) Has the patient been exposed to tuberculosis and if so, when, where, and to what extent? Has there been a family history of tuberculosis and was the patient exposed to the members of his family who suffered from the disease?

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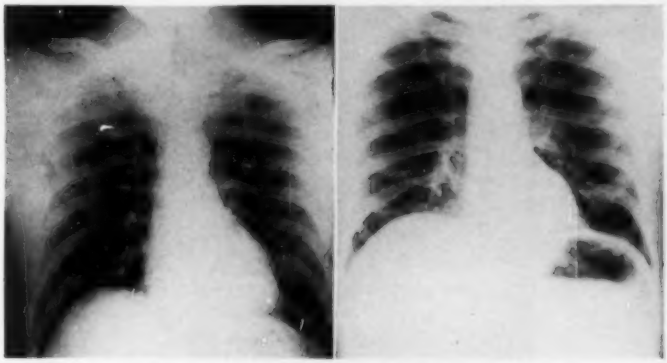
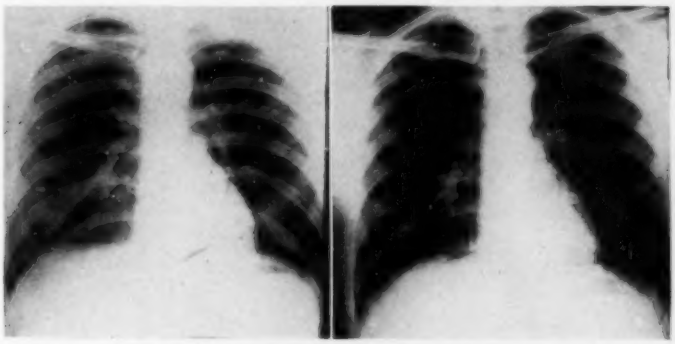
Case 1b: The patient was a white male, age 24 years, who entered his internship on July 1, 1947. His chest x-ray films at that time were normal, and he had a previous negative tuberculin reaction. In January, 1948 his routine hospital chest x-ray film revealed a lesion in the right base. A tuberculin test was now strongly positive. He developed pleural effusion and ultimately parenchymal tuberculosis. The patient had served on the general wards of a hospital that had no tuberculosis control program. In all likelihood, he received the infection from a patient with unrecognized pulmonary tuberculosis who was in the hospital for the treatment of a non-tuberculous disease. This case illustrates well the value of the history concerning the previous chest x-ray films and the results of previous tuberculin tests. It further reemphasizes the importance of a



CASE 1a: An instance of atypical pneumonitis associated with hemoptysis that was believed to be pulmonary tuberculosis. At the time upper respiratory infections were common in the community.



CASE 1b: This patient had known that his previous chest films were normal and that his tuberculin test had been negative. Unfortunately the previous films had been destroyed. The information, however, was valuable in interpreting the film of January 1945. Subsequent events established the diagnosis of tuberculosis.

CASE 1c: The diagnosis in this instance was made by the history of the patient's interest in pigeons. The laboratory studies immediately confirmed the suspicion of ornithosis.

history concerning the absence of previous chest diseases as well as the knowledge of actual or potential exposure to lung infection.

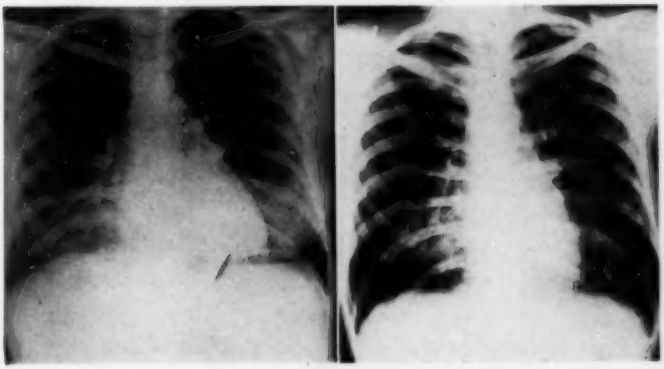
c) The occupational history should emphasize the possible exposure to irritating dusts, vapors, etc.

Case 1c: The patient was a 15 year old white male who entered the hospital on January 10, 1949 with a diagnosis of atypical pneumonia. The history revealed that he was interested in pigeons and that before the onset of this illness he cared for sick pigeons. In addition, he cleaned out the pigeon coop. Bacteriological investigation establishes the diagnosis of psittacosis. This case illustrates the importance of the history relative to the avocation as well as the vocation.

d) Was it possible for the patient to be exposed to fungi or has the patient resided in or traveled through known endemic areas?

Case 1d: A white female, age 25 years, whose routine chest x-ray film on August 1, 1946 demonstrated scattered calcification throughout the lungs. Films of her chest made during 1935-36 and 1938 were available for comparison and showed the same condition as on August 1, 1946. The diagnosis of tuberculosis could not be established to explain the calcification. The patient, however, had resided in an area where there was a high incidence of histoplasmosis. It was presumed that the calcification represented the residual of a histoplasmosis infection. At the time of examination no material was available for doing the histoplasmin skin tests. In February, 1948 a re-ray revealed a small infiltration in the right apex. The lesion disappeared and we have no knowledge as to its etiology. The patient remains well. Her skin test to histoplasmin is strongly positive and the Mantoux test is negative.

e) What is the racial extraction of the patient? It is well known that certain races are more prone to tuberculosis than are others.



CASE 1d: Scattered calcification was known to be present on previous chest x-ray films. These films were obtained for comparison and there had been no change in the shadows. Repeated tuberculin tests have been negative and the skin tests for histoplasmosis have always been positive. The patient had resided in an area wherein histoplasmosis has been endemic.

f) Has the patient ever before had a chest x-ray film? If so, for what purpose, and can it be obtained for comparison purposes?

Case 1b: See above.

g) Has the patient ever had a tuberculin test? What was the result?

Case 1b: See above.

h) Has the patient ever had a previous chest disease?

Case 1b: See above.

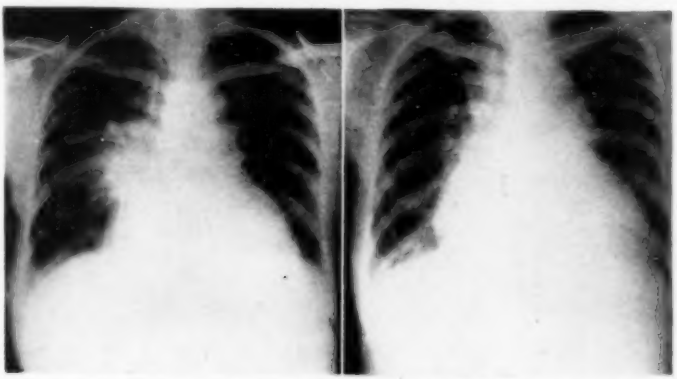
2) What constitutes the physical examination?

The physical examination should be made with the patient completely disrobed and in a well illuminated room. It should include the examination of all organs and systems in the body and every orifice should be examined.

Case 2: A white married female age 46 years entered the hospital in July, 1946 because of hemoptysis. She had been a known hypertensive for many years. Recently she suffered an episode of hypertensive encephalopathy from which she made an uneventful recovery. She had noticed dyspnea on exertion for some two weeks before her entrance to the hospital. On the day of admission while walking she developed severe dyspnea followed by hemoptysis. The x-ray film on admission, July 26, 1946, was interpreted as showing evidence of possible primary bronchogenic carcinoma. The physical examination, however, revealed congestive heart failure and the patient was jaundiced. Under the circumstances, it was felt that the lesion in the right lung was probably a pulmonary infarction. Subsequent events and examinations proved this to be so. In this case the history and physical examination led to the solution of the problem.

3) What is the minimum amount of laboratory work indicated?

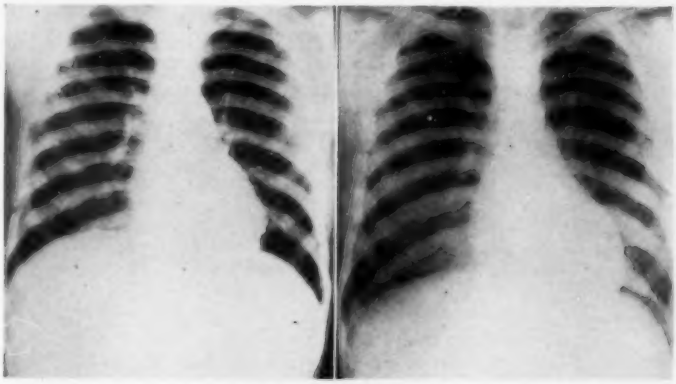
It is suggested that the minimum amount of laboratory work should be:



Case 2: Pulmonary infarction which was first thought to be a bronchiogenic carcinoma.

a) Hemoglobin

Case 3a: A 15 year old white male who entered the hospital in July, 1942 because of anemia and hemoptysis. The diagnostic survey established the presence of severe anemia. He had had recurrent episodes of hemoptysis. Detailed hematological studies led to the diagnosis of primary pulmonary hemosiderosis.



CASE 3a: A young man who had repeated pulmonary hemorrhages and in whom the diagnosis of primary pulmonary hemosiderosis was finally suggested.

b) White blood count and differential blood count

Case 3b: A white woman, age 33 years, entered the hospital in November, 1942 with a diagnosis of pneumonia or pulmonary tuberculosis. The chest lesions were accompanied by leukocytosis and an eosinophilia at times of 30 per cent. The fugitive nature of the infiltration, its recurrence and complete healing suggested the diagnosis of eosinophilic pneumonitis. Further laboratory studies established this diagnosis.

c) Sedimentation rate

d) Urinalysis

e) Wassermann test

f) Agglutination test for undulant fever in endemic or epidemic areas. Other laboratory procedures should be ordered when indicated.

4) What is the role of the tuberculin test (Mantoux test)?

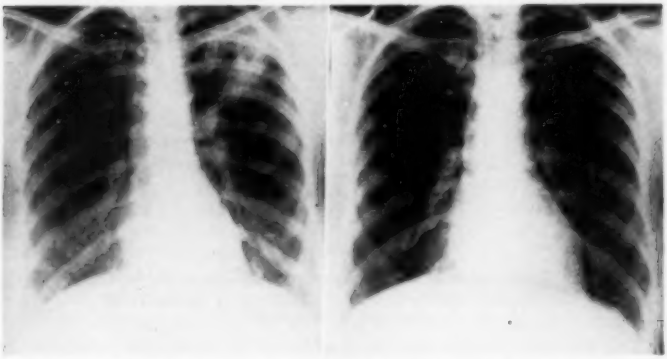
This is the most valuable test known to determine the existence of an infection by tuberculosis. The test for accuracy is dependent upon:

a) Potent material in proper dilution

b) Proper intradermal injection

c) Proper interpretation of the test at the end of 48 to 72 hours.

The test should be read by the degree of induration and not by the zone of erythema. For practical purposes it is not necessary to give the degree of reaction but rather to report the test as either positive or negative. Any induration exceeding 5x5 mm. is considered a positive reaction. Should the test prove positive, the patient should have a chest x-ray examination and this should be repeated once yearly if no disease is found on the original film. Those people who have a negative Mantoux reaction should be retested not less than once yearly. When indicated, other skin tests may be applied. A positive tuberculin test does not mean clinical tuberculosis.



CASE 3b: An instance of pneumonitis associated with eosinophilia.

5) What is the role of the roentgenologist?

The roentgenologist has an important role in the screening of chest x-ray films. In making his report he should not be too positive in his diagnosis but rather describe the lesions seen and then suggest the possible diagnosis. When indicated, the roentgenologist should feel at liberty to suggest other specialized x-ray procedures to help in making the diagnosis. Wherever possible, both he and the clinician should determine whether other chest x-ray films have previously been made on the patient in question, and if so, an effort should be made to obtain the films for comparison. It must be emphasized that serial x-ray films of the chest are often more valuable than a single film. Follow-up x-ray films should be made on every patient who has a chest lesion and/or who has a positive Mantoux test. The maximum period between films should not exceed one year. X-ray films should always be required at the time of discharge of patients from the hospital after apparent recovery from acute chest diseases. Most important, *make use of the roentgenologist as your consultant.*

6) What is the minimal laboratory work indicated to determine the presence of the tubercle bacillus?

It is necessary to know that the material being submitted for examination actually has come from the lungs and that it is not simply saliva or nasal discharge. It is suggested that three successive 24 hour sputum specimens be submitted for smears, culture and/or guinea pig inoculation. If the attending physician suspects that other organisms than the tubercle bacillus are causing the chest lesion, he should so inform the laboratory personnel. When the patient is not raising sputum, gastric washes should be done and the material submitted for both guinea pig and/or cultural investigation. The sputum material should also be submitted to the laboratory to determine, in addition, whether other organisms, parasites, or the like, are present. Exudates, such as pleural fluid, etc., should also be submitted for laboratory investigation. Do not overlook the possibility of finding malignant cells in sputum, exudates, etc.

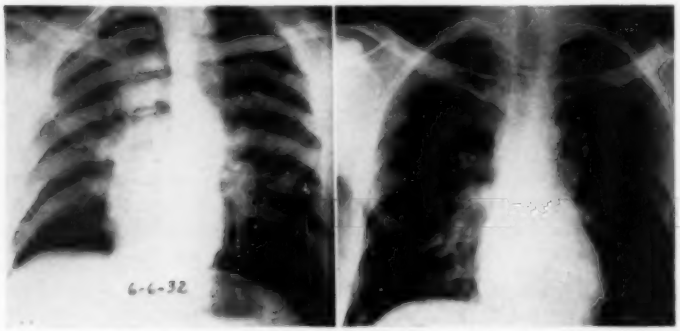
Case 6: A white male, age 54 years, entered the hospital in June, 1947 with the diagnosis of pneumonitis or pulmonary tuberculosis. The bacteriological survey excluded tuberculosis, but it established the cause of the lung lesion to be due to a Friedlaender's infection. The patient ultimately recovered from the disease.

CASE 6: This upper lobe lesion was the result of an infection by the Friedlaender's organism.

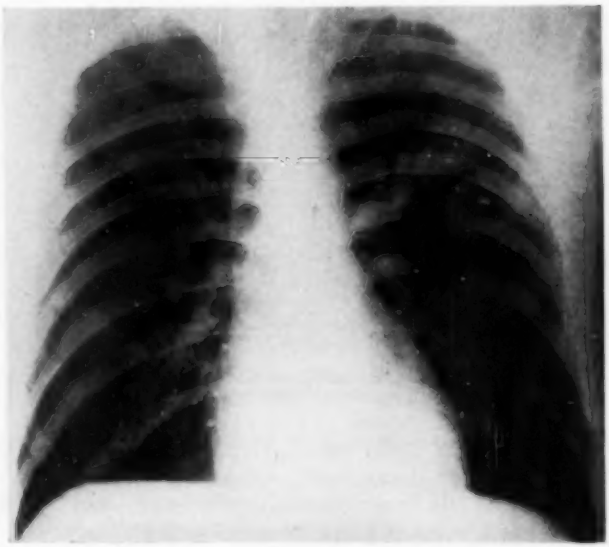
7. What other procedures may be used to diagnose chest lesions?

There are a great many highly specialized investigations that assist in making the diagnosis of a chest lesion. Some of these, such as bronchoscopy, bronchograms, kymography, and the like, can only be done in centers especially equipped for such studies. When these specialized studies are indicated, the attending physi-

cian should refer his patient to a physician or to an institution equipped to carry out such investigations. Should the bacteriological diagnosis not be established immediately, and the chest infiltration in any way suggests a malignancy, the patient should immediately be subjected to an exploratory thoracotomy for a diagnosis as well as treatment.



CASE 7a: Sarcoidosis diagnosed by lymph node biopsy.



CASE 7b: This lesion in the left apex was ultimately proven to be a congenital pulmonary arteriovenous fistula.

Case 7a: A white male, age 25 years, was seen in June, 1932 at which time a chest x-ray film revealed the presence of a hilar mass, and physical examination revealed generalized lymphadenopathy. The diagnostic survey did not explain the nature of the disease and biopsy of a lymph node was made. The histology was characteristic of sarcoidosis. Here a biopsy was needed to arrive at a definite conclusion.

Case 7b: A white male, age 29 years, entered the hospital on June 6, 1944 because of a high temperature, petechial hemorrhages and conclusions. A chest x-ray film on June 10, 1944 showed an infiltration extending out from the left hilus into the left apex. It suggested the appearance of either pneumonia or tuberculosis. The diagnostic survey did not establish the cause of the infiltration. The patient returned in December, 1946 and a systolic bruit was heard over the left apex. The quality of the bruit changed with respiration and the examiner suggested the diagnosis of a pulmonary arteriovenous fistula. Special x-ray studies confirmed this impression, and a review of the entire record brought out a familial history of telangiectasis, thence the ultimate diagnosis of congenital familial telangiectasis was made. The patient refused surgical treatment. In this instance the roentgenologist by virtue of a special x-ray film study played an important part in the solution of this problem.

8) What should be the follow-up procedure in the patient in whom chest lesions have been found?

It is recommended that the private physician make every effort to see that such patients be re-examined periodically. It is the duty of the private physician to use every facility at his command to have his patient's return for clinical and x-ray examinations. If necessary, he should call upon the public health nurse in his locality or the public health officer to aid him in the periodic follow-up of the patient with a chest disease.

SUMMARY

The diagnosis and work-up of a patient with an abnormal x-ray shadow of the chest is dependent upon, first of all, a detailed history and physical examination. Second, it is important to remember that the roentgenologist's diagnosis is only an impression, and that although the description of the lesion as he sees it is accurate and his interpretation of the cause of the lesion may be highly correct, he still cannot make a histological or bacteriological diagnosis from the film. The ultimate diagnosis remains the province of the physician and in most instances the diagnosis can be established in the manner outlined above.

RESUMEN

El diagnóstico y el estudio del paciente con una sombra anormal en la radiografía torácica dependen, en primer lugar, de la historia y del examen físico rutinarios. En segundo lugar, es importante

recordar que el diagnóstico del roentgenólogo es solamente una impresión y que, aunque la descripción de la lesión que él ve es exacta y su interpretación de la causa de la lesión puede ser bastante correcta, aún así le es imposible hacer una diagnóstico histológico o bacteriológico basado en la película. El diagnóstico final queda en manos del médico y en la mayoría de los casos puede hacerse de la manera aquí bosquejada.

RESUME

Le diagnostic et l'étude complète d'un malade qui est atteint d'une ombre radiologique anormale à l'examen tu thorax dépendent avant tout de l'histoire de sa maladie, et d'un examen physique bien mené. En second lieu, il est important de toujours se souvenir que le diagnostic du radiologiste n'est qu'une impresion et il ne peut donner avec la seule aide du film un diagnostic histologique et bactériologique. Le diagnostic en dernier ressort reste le privilège du médecin et doit être conduit selon les règles que l'auteur a rappelées.

An Aortic Deformity Simulating Mediastinal Tumor: A Subclinical Form of Coarctation

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The benign or malignant nature of a mediastinal mass is often determined by the presence or absence of accompanying pulmonary or more remote lesions or at times by the response to a trial dose of radiation therapy. The stimulus imposed by developments in the field of thoracic surgery, however, has served to emphasize the need for more definitive diagnosis of mediastinal masses in order to segregate the *operable* from the *nonoperable lesions*. This can only be accomplished by an increasingly critical study of such lesions through utilization of a variety of technics, both old and new.

In the past two years we have encountered three instances of a congenital anomaly of the aortic arch and the first part of the descending aorta which so closely simulated a superior mediastinal tumor that thoracic exploration was necessary in the first case to clarify the nature of the lesion. In the two subsequent cases the diagnosis was suspected from the roentgenographic appearance and confirmed by more detailed studies including angiocardiography.

In all three patients the mediastinal mass was an accidental discovery as none of them had symptoms referable to the chest or mediastinum. There was no clinical evidence of abnormal pulsation of the vascular tree or of collateral circulation. The heart was not abnormally enlarged and hypertension was not present. There was no inequality of the peripheral pulse and no thrills were palpable.

In this anomaly (Figure 1) the aortic arch distal to the origin of the left subclavian artery recurves sharply upon itself toward the pulmonary artery, then kinks abruptly and again proceeds laterally to resume the usual course of the descending aorta. The result is a deformity of the aorta resembling a figure "3." In the usual postero-anterior roentgenogram of the chest this produces a shadow of smooth rounded contour superimposed and superior to what appears to be the normal aortic knob but which is in reality one of the two projections of the deformed aorta.

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This abnormality was clearly visualized at operation in one case, at which time a small patent ductus arteriosus was exposed and ligated directly opposite the greatest medial deflection in the tortuous aorta. There was minimal decrease in the diameter of the aorta in this region and the anomaly was considered to be an example of a grade one coarctation of the aorta mainly because the kinking deformity was similar, but more accentuated, than that noted in most instances of true coarctation. Because of the similarity of the x-ray appearance of the second and third cases to that of the first, further studies were carried out which revealed similar if not identical aortic deformities when viewed in the left anterior oblique roentgenogram and by angiocardiographic tech-

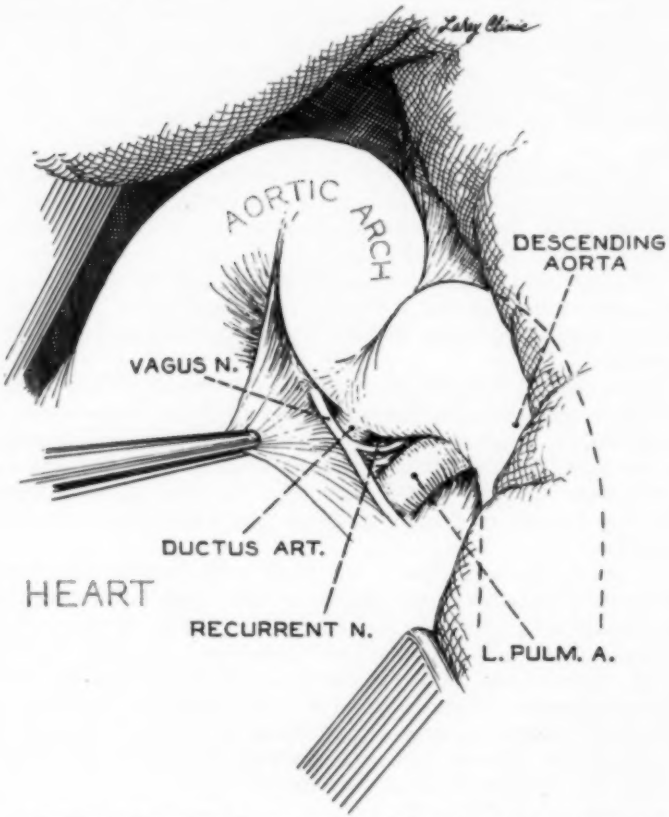

FIGURE 1: Schematic drawing showing "kinked aorta" and anatomical relationships (See Figure 4).

nics. The presence of a patent ductus arteriosus in these cases was neither confirmed nor ruled out. However, there was no clinical evidence of any other vascular anomaly.

A brief summary of the clinical and roentgenographic observations in these cases, together with the operative findings in the first, will serve to illustrate the essential features of this deformity.

Case 1: A 58-year-old male barber was first seen at the Lahey Clinic in October 1947 at which time he complained of epigastric distress relieved by alkali and accentuated by alcohol. There were no symptoms referable to the chest. Physical examination was essentially negative. The heart was not enlarged, there were no murmurs and no abnormal vascular pulsations. The blood pressure in the right arm was 115/75 and in the left arm 115/70. A serologic test for syphilis was negative. Barium studies of the upper intestinal tract revealed cardiospasm. Routine chest films and fluoroscopy were reported as showing the heart to be normal in size and the lungs to be clear. There was a rounded circumscribed, soft tissue mass measuring 5.5 cm. in diameter in the superior mediastinum overlying the aortic arch but somewhat more to the left of the midline (Figures 2 and 3). The mass appeared to show transmitted but no expansile pulsations. The tracheal bifurcation was slightly displaced to the right. The esophagus was not deviated.

A tentative diagnosis of Hodgkin's disease with mediastinal involvement was made and 2400 r. of radiation therapy was administered through an anterior port. Subsequent roentgenograms taken in one, two and four months, however, showed no change in the appearance of the mediastinal tumor mass, and it was then thought that an exploratory operation was indicated. This was performed in May 1948.

The left thorax was explored through a posterolateral incision. Upon exposing the upper mediastinum, the mass shown on the roentgenogram could be clearly seen as an unusual prominence of the arch of the aorta just distal to the origin of the left subclavian artery. This was identical to the deformity of the arch seen in coarctation of the aorta. The mediastinal pleura was then opened and the remainder of the arch visualized more clearly (Figure 4). Distal to this prominence the aorta swung sharply to the right and back again, forming a compound reverse curve similar to the deformity of coarctation, but with only slight narrowing or stenosis at the point of attachment of a small patent ductus arteriosus. The entire deformity gave the appearance of a buckling of the aorta resulting from the pull of a contracted ductus arteriosus. Since there was not a significant degree of stenosis or narrowing at this point, and since the patient did not have hypertension, resection was not performed. However, the thick-walled patent ductus arteriosus was sectioned to see whether releasing the aorta at this point would cause it to return to the normal position. Since the contour of the aorta did not change, the operation was terminated, the mediastinal pleura was sutured and the thorax closed.

A roentgenogram taken three months after operation showed no change in the area of density. The clinical course since the operation has been uneventful.

Case 2: A 33-year-old meat cutter entered the hospital in May 1949, immediately following the sudden onset of a traumatic left radial palsy.

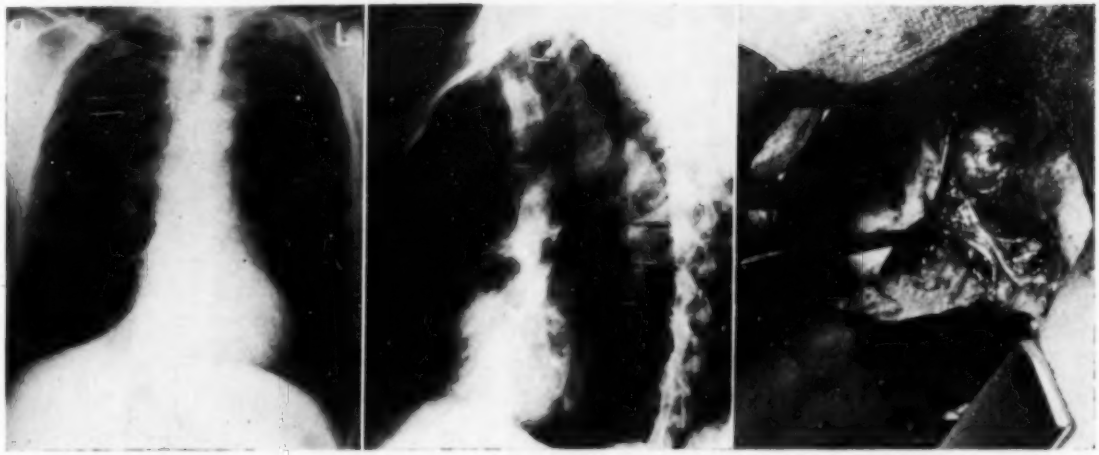

FIGURE 2 FIGURE 3 FIGURE 4

Figure 2 (Case 1): Postero-anterior view demonstrating a soft tissue density in the superior mediastinum overlying what appears to be a normal aortic knob.—*Figure 3 (Case 1):* Left anterior oblique view showing the marked tortuosity and buckling of the aortic arch and first portion of the descending aorta.—*Figure 4 (Case 1):* Photo taken at operation showing "kinked aorta" and anatomical relationships (See Figure 1).

There were no symptoms referable to the chest. Physical examination revealed a swollen, painful left hand and arm, with paralysis. Chest examination showed the lungs to be clear and the heart to be normal in size. A faint systolic murmur was heard just medial to each scapula. There were no abnormal vascular pulsations. The blood pressure in the right arm was 120/85, in the left arm 126/82, in the right leg 140/95 and in the left leg 138/108. A serologic test for syphilis was negative.

A routine chest film in the postero-anterior position showed a clearly outlined shadow, 5 cm. in diameter, of soft tissue density overlying the left portion of the aortic arch (Figure 5). It could not be separated from the arch in stereoscopic, right and left oblique or left lateral projections. Fluoroscopically the mass showed no direct pulsation. The cardiac silhouette and lung fields were normal and there were no rib erosions. Roentgenograms of the chest taken elsewhere three years previously were available for comparison. Review of these roentgenograms showed an identical soft tissue shadow overlying the left portion of the aortic arch.

The radial palsy was treated by sympathetic nerve block with gradual symptomatic improvement. Because of the similarity of the roentgenologic appearance to that noted in the previous case, angiocardiographic studies were carried out after an interval of two weeks. These demonstrated that the above described soft tissue shadow increased in density and sharpness of outline when there was a maximum of opaque medium in the aortic arch and thoracic aorta. There was a distinct deviation from normal in the contour of the arch and descending thoracic portion of the aorta which described a tortuous folding of the aorta upon itself in the upper mediastinum (Figure 6). No narrowing of the diameter of the aorta at any point was observed.

Case 3: A 46-year-old housewife entered the Lahey Clinic in October 1949 complaining of a chronic cough of one year's duration. She had a long history of sinusitis and functional complaints. There were no other symptoms referable to the chest or cardiovascular system. On physical examination the lungs were clear and the heart was normal in size. There was a grade 2 harsh systolic murmur loudest in the pulmonic area and over the left clavicle. It was transmitted to the right second interspace, to the vessels of the neck, and into the upper back. Abnormal pulsations were not detected and the pulses in all extremities were normal. The blood pressure in the right arm was 115/65 and in the left arm 110/65. The serologic tests for syphilis were all negative.

Fluoroscopic and roentgenographic studies of the thorax showed the heart to be normal in size and position. The lung fields were clear except for partial atelectasis of the left lower lobe. An oval soft tissue density measuring 8 cm. in length was present in the superior mediastinum overlying and just below the level of the aortic arch. This density was superimposed on the fifth, sixth and seventh thoracic vertebrae. An esophagram showed displacement of the esophagus to the right and anteriorly (Figure 7) and there was some compression of the left main bronchus causing the partial left lower lobe atelectasis previously described.

A roentgenogram taken elsewhere one year previously was available for comparison and revealed the identical density in the superior mediastinum.

FIGURE 5 FIGURE 6 FIGURE 7

Figure 5 (Case 2): Postero-anterior view illustrating the double aortic shadow produced by two projections of a tortuous kinked aorta.—*Figure 6 (Case 2):* Left anterior oblique angiocardiogram showing in profile the tortuous curving of the aorta.—*Figure 7 (Case 3):* Left anterior oblique view demonstrating the anterior displacement of the barium-filled esophagus.

Two months later the density had not changed in appearance and an angiocardiogram was performed. For technical reasons this was somewhat unsatisfactory but did reveal what appeared to be a slight narrowing of the transverse aortic arch. The head of the contrast medium was seen to fade imperceptibly into the region of the oval mass.

Comment

It is not the purpose in this discussion to consider all of the possible lesions that could be concerned in the differential diagnosis of a superior mediastinal mass. Instead we wish to suggest that there is yet an additional lesion which so far as we are aware has not previously received attention in the literature. This is the double curving or buckling of the aorta which in the postero-anterior projection of the roentgenogram gives the appearance of a soft tissue mass superior to and overlying a small or normal aortic arch. The diagnostic importance of this lesion lies in its essentially benign nature. Operation should be avoided and nothing more than impressing upon the patient the harmlessness of the lesion should be considered.

Abbott[1] in her review of congenital cardiac disease has not mentioned this type of aortic deformity and the only case we have been able to find in the literature which resembles those herein described is one briefly summarized by Reich[2] in his book on diseases of the aorta. The patient he described was a healthy 40-year-old man who had a routine chest roentgenogram taken upon discharge from the Army. This revealed a mediastinal mass of undetermined nature. A postero-anterior esophagram showed compression and displacement of the esophagus to the right and an angiocardiogram revealed a tortuous, hypoplastic aortic arch forming a superior convexity and below this a "slight coarctation" of the aorta with aneurysmal dilatation of the descending aorta. The published oblique views of this case show a double curved deformity of the aorta identical to that we have described.

Short of a thoracotomy the diagnosis has, by necessity, to be made entirely by roentgenographic means but the absence of associated clinical symptoms is of great value. In the cases we have observed there were no physical signs except for the presence of a systolic murmur heard in two cases posteriorly, lateral to the spine. On the standard postero-anterior chest film the soft tissue shadow ranged in diameter from 5.5 cm. to 8 cm. In each instance the shadow overlay what was interpreted to be the aortic arch. Fluoroscopically, pulsations were absent in one case and were said to be transmitted, not expansile, in another. In one instance (Case 2) the soft tissue mass could not be "thrown off" the aorta in any projection but no pulsations were noted in the mass. The oblique views, especially

the left anterior oblique, were of most value in outlining the character of the lesion (Figs. 3 and 6). In this view the entire ascending aorta, the arch and the descending aorta can be separated from the adjacent structures, including the spine. The actual tortuous course of the aorta was clearly revealed in one of the cases (Case 1) by this technic without the need for more complicated studies.

Esophagrams revealed no characteristic or specific deformity in these cases. In two instances there was no esophageal deviation and in the third (Case 3) there was displacement of the esophagus to the right and anteriorly (Fig. 7). The latter was similar to the esophageal displacement described by Fleischner[3] as a result of dilatation of the aorta after coarctation. It is possible that this case may have a more definite narrowing (coarctation) and therefore postcoarctation dilatation than do the other two cases.

Although angiocardiography is not essential to the diagnosis it may be of assistance, and was carried out in two of the present cases. Because of technical difficulties it was somewhat inconclusive in one case and definitely clarifying in the other.

Among the vascular abnormalities in the superior mediastinum which may be confused with this lesion the foremost is true aortic coarctation. In this condition the actual constriction of the vessel is often difficult or impossible to visualize even by angiocardiography. True coarctation may be differentiated by finding one or more of the following: (1) dilatation of the ascending aorta; (2) cardiac enlargement; (3) evidence of a collateral circulation manifested by notching of the rib margins and clinical signs and symptoms of abnormal vascular pulsations in the suprascapular or intercostal areas; (4) hypertension in the upper one half of the body and (5) the absence of a conspicuous aortic knob. This lesion may also be confused with aneurysms of the ascending aorta, of the aortic arch or of the first portion of the left subclavian artery. Fluoroscopic examination as well as the detection of abnormal pulsations and thrills, serologic tests, and so forth, should serve to differentiate these conditions. Actual elongation of the aorta into the superior mediastinum, as seen in hypertension and arteriosclerosis, can easily be differentiated. In these instances a double overlapping shadow is not produced but rather in the posteroanterior position the arch is elevated, the aortic knob is prominent, and the left border of the descending aorta is displaced to the left. In the lateral or oblique positions the elongation is recognized by an increase in the radius of the arch of the aorta and displacement of the descending aorta posteriorly. Abnormal elongation of the aorta in the region of the arch, as described by Khoo[4] in a young boy, and in the thoracic aorta as outlined by Corcoran and

Coleman[5] would be difficult to confuse with the deformity of the aorta described.

So-called subclinical coarctation of the aorta has been established as a pathologic entity. Reifenstein, Levine and Gross,[6] in a review of a large amount of postmortem material, have found that about one-fourth of patients with varying degrees of coarctation have only mild to moderate symptoms or none at all and in many of these instances the presence of the constriction is totally unsuspected until the time of autopsy.

It is likely that the three cases described form a sub-variety of the latter group of coarctations. In these three cases there is an accentuation of the double-curved deformity reminiscent of the kinking and angulation of the aorta from the pull exerted by the ligamentum arteriosum in true coarctation. In the latter condition, however, there is more or less narrowing of the aorta usually at the point of greatest medial deflection, whereas in our cases the constrictive (coarctation) element is apparently minimal or lacking and the external deformity is exaggerated and predominant.

Among the theories advanced to explain the constrictive aortic anomaly in coarctation is the classical description by Craigie[7] in 1841 who postulated that the obliterating action which normally occurs in the ductus arteriosus has been "for some peculiar cause" prolonged into the aorta, thereby giving rise to contraction and then to obliteration of the coats of that great vessel. This has been termed the *skodaic theory* and has been widely accepted. An additional mechanical factor comes into play in the majority of cases and likely is the most important portion of the process as far as the present cases are concerned. This factor is the traction exerted at the point of coarctation by an abnormally short and small patent ductus arteriosus (ductus Botalli), or ligamentum arteriosum when it persists as a thick fibrous cord. Either of these processes would manifestly increase the kinking of the descending aortic arch by the traction exerted at the point of coarctation. At times this mechanical traction has been so strong as to produce a tent-shaped aneurysm of the aortic wall with its apex toward the ligamentum. Minor degrees of such a mechanical pull, on the other hand, are undoubtedly represented by the "dimpling" of the medial aortic wall so often seen at the point of attachment of the obliterated ductus without actual coarctation or traction deformity.

In the three cases presented in this communication we have visualized the buckling deformity as one of *contraction without constriction* (or with minimal constriction). In other words, an abnormally short ductus or ligamentum arteriosum has caused a marked traction deformity on the aorta, the pull of which has been approximately uniform about the aorta so that little tenting of the

medial wall has been produced and instead a uniform tortuous double curvature of the distal aortic arch has occurred. The "constricting processes" which are present in true coarctation were either absent or minimal in our cases.

SUMMARY

Three examples of an unusual aortic deformity have been described. All were found in adults without clinical signs or symptoms referable to the chest. In all three, the anomaly was an incidental finding on routine roentgenologic examination of the chest.

The deformity appeared in the postero-anterior chest roentgenogram as a mediastinal soft tissue density overlying a normal aortic arch. The true nature of the aortic abnormality was best seen in the left anterior oblique chest position.

In one case in which operation was performed there was a kinking deformity of the aorta toward the pulmonary artery at the attachment of a short ductus arterious. Minimal narrowing of the aorta was present.

This buckling deformity has been interpreted as a subclinical coarctation of the aorta in which the external traction or pulling deformity predominated and the constricting element was minimal or absent. The scanty literature on the subject is discussed.

RESUMEN

Se describen tres ejemplos de una deformación aóstica poco común.

Todas se han encontrado en adultos sin signos físicos o síntomas en el tórax. En los tres la anomalía fue hallada incidentalmente en examen radiológico de rutina.

La deformación apareció en la radiografía postero-anterior como una densidad de tejido blando mediastinal sobre el arco aórtico.

La naturaleza de este hallazgo se comprobó mejor en oblicua anterior izquierda.

En un caso en el que se realizó intervención quirúrrgica había una torcedura de la aorta hacia la arteria pulmonar en el abocamiento de un conducto arterioso corto. El estrechamiento de la aorta era mínimo.

Esta deformación en enrollamiento de la aorta ha sido descrita como una coartación subclínica en la que predominar la tracción externa y el elemento constrictor era mínimo o inexistente.

Se discute la escasa literatura que hay sobre este asunto.

RESUME

Les auteurs donnent trois exemples d'une déformation inhabituelle de l'aorte. Toutes furent constatées chez des adultes qui

n'avaient aucum signe clinique d'affection thoracique. Dans les trois cas, l'anomalie fut une découverte d'examen radiologique systématique du thorax.

La déformation apparut sur le cliché de face comme une ombre médiastinale de faible densité, recouvrant une convexité aortique normale. La véritable nature de cette anomalie fut mieux constatée en oblique antérieure gauche.

Dans un cas qui fut opéré, il y avait une déformation aortique au point d'attachement le l'artère pulmonaire avec un court canal artériel. On notait un rétrécissement extrêmement discret de l'aorte.

Cette déformation a été inerprétée comme un rétrécissement infra-clinique de l'aorte dans lequel la déformation par traction était prédominante tandis que les conséquences de la sténose étaient minimes ou absentes. Un court exposé de la littérature concernant ce sujet est mis en discussion.

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A Study of the Pulmonary Circulation in Man*

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In the last two and a half years we have utilized catheterization of the heart to study the pulmonary circulation in man. Our observations may be divided as follows: (1) method, (2) results in cases of bronchial asthma, and (3) results in cases of cor pulmonale, (4) the action of drugs, (5) the immediate effect of pneumonectomy, and (6) the effect of pulmonic regurgitation.

Method

The technique of Bloomfield, et al.,[19] and Cournand, et al.,[1] was used to place a catheter in the pulmonary artery. The phase of respiration, and the blood pressure levels in the right auricle and right ventricle and in the brachial or femoral artery, together with the electrocardiogram, were recorded simultaneously by means of a Brush six-channel, direct writing oscillograph. Pressures[2] were measured by Statham gauges, the phase of respiration was registered on a strain gauge, the cardiac output was measured by the direct Fick principle, and the oxygen content of the blood was ascertained either spectrophotometrically or by the micro method of Scholander. Duplicate estimations of oxygen content were made. Oxygen consumption was ascertained by means of a reciprocating spirometer or an especially modified gas meter. Unless otherwise stated, all patients were studied in the basal state except that 0.09 gm. of a rapidly acting barbiturate, either Seconal or Nembutal, was administered one hour before the observations were made. The administration of the barbiturate has been shown to stabilize basal cardiac output.[3] Figure 1 shows the catheter in a branch of the right pulmonary artery.

The Pulmonary Circulation in Cases of Bronchial Asthma

A patient with cor pulmonale who, in addition, had had bronchial asthma for many years developed an attack of severe bronchial asthma at the time of catheterization, and it was found that the pulmonary arterial pressure rose from 67/27 mm. Hg. to 145/50 mm. Hg. This prompted us to study the dynamics of the pulmonary

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circulation in other cases of bronchial asthma, and data on 10 cases are presented (Figure 2).

These patients either had a spontaneous attack of asthma or one was induced by giving 5 to 10 mg. of mecholyl subcutaneously. Moll[4] has pointed out that increased susceptibility of the bronchi to mecholyl is observed in both the continuous and the paroxysmal type of bronchial asthma. It is of interest that patients who have been free from asthma for months or even years may still be susceptible to mecholyl. The attacks of asthma induced by mecholyl are probably not similar in all respects to spontaneous attacks of bronchial asthma, but the clinical manifestations are the same.

The effects of aminophyllin and adrenalin were observed in this group of patients during an asthmatic attack. Aminophyllin (0.5 gm. in 20 cc. of distilled water) was given intravenously over a period of five minutes. It is essential that 5 minutes be taken for the injection in order to eliminate the systemic reactions which occur when aminophyllin is injected rapidly. Adrenalin (1-1000 solution in doses of 0.3 to 0.5 cc.) was injected intramuscularly. Figure 3 shows a typical response.

Our data suggest that aminophyllin acts in man as it does in animals; namely,[5] it dilates the pulmonary arterioles and reduces peripheral resistance, thus causing a fall in pulmonary arterial pressure.

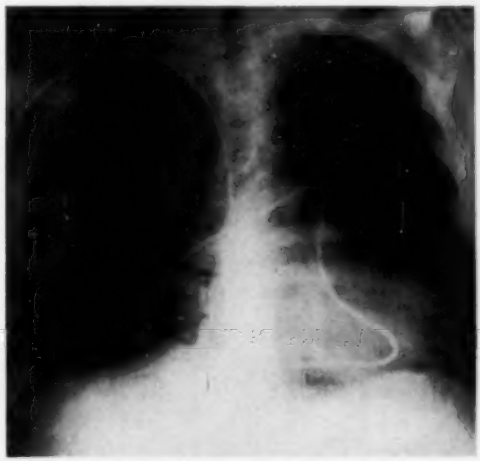

FIGURE 1: Is a teleoroentgenogram of the heart and shows an intracardiac catheter placed in a branch of the right pulmonary artery.

FIGURE 2: Is a summary of the hemodynamics in 10 patients with bronchial asthma. During an attack of asthma, the average rise in pulmonary systolic pressure was 23.4 per cent and the average rise in pulmonary diastolic pressure was 38.2 per cent. Note that the adrenalin and aminophyllin pressures respond as shown when taken 10 minutes after the administration of the drug.

Patient Sex Age	P. A. PRESSURE S/D mm. Hg	Mean mm. Hg	PUL. RESISTANCE dynes/cm5/sec.	F. A. PRESSURE S/D mm. Hg	Mean mm. Hg	AORTIC FLOW L./min.	SYSTENIC RESISTANCE dynes/cm5/sec.
D.N. M 65	22.5/7	14.5	1869	112/57	66	6.2	850
After mech.	25/8	15.8	2049	95/37		5.0	1076
After adren.	21/6.4	11.1	1310	123/61	86	8.6	800
After amino.	19/52	8.7		114/59	77		
E.W. M 17							
Before med.	19/5	9.5	1095	98/56	71.2	6.9	817
After mech.	25/6.2	14.3	3368	108/62	81.8	3.3	1928
After amino.	18/3.7	8.2	1070	130/87	108	3.6	2339
After adren.	22/3.5	8.8	1094	120/80	87	7.1	969
E.Mc. F 36							
Before med.	29/10	19.7	1875	142/96	116	8.4	1095
After mech.	32/7.5	26	2442	128/91	110	8.5	1024
After adren.	27/8.7	17	1932	153/102	123	7.1	1389
After amino.	19/7	9.6	1015	153/102	120	7.5	1268
L.J. M 47							
Before med.	24/10	18.1	1502	175/107	130	9.6	1075
After mech.	29/18	25.3	2516	195/127	149	9.1	1305
After amino.	19/10.2	16.6	1621	190/112	125	8.1	1224
After adren.	25/14	19.6	1781	155/101	123	6.2	1575
R.S. F 38							
Before med.	32/14	24.4	504	102/55	78	3.8	1643
After mech.	43/20	29.2	567	126/65	88	4.1	1708
After amino.	15/8	14.6	350	105/67	87	3.3	2089
After adren.	27/13	23.8	313	115/57	87	6.1	1135

Patient · Sex Age	P. A. PRESSURE S/D mm. Hg	Mean mm. Hg	PUL. RESISTANCE dynes/cm5/sec.	F. A. PRESSURE S/D mm. Hg	Mean mm. Hg	AORTIC FLOW L./min.	SYSTEMIC RESISTANCE dynes/cm5/sec.
F.N. M 57							
Before med.	31/14.7	21.4	259	195/85	117	6.3	1469
After mech.	32/13	20.5	349	185/85	115	4.5	2010
After amino.	22/14	18.5	206	210/105	150	6.7	1784
After adren.	26/19	22.3	249	185/82	118	7.1	1321
L.B. F 45							
Before med.	35/11	29	386	142/80	105	6.0	1398
After adren.	24/5	14.7	195	118/68	88	6.0	1172
After mech.	36/10	22.5	159.8	99/47	70	7.8	829
After amino.	15/6.4	14.3	198	92/58	74	5.7	1026
F.W. M 44							
Before med.	25/10	17.8	134	146/73	111.5	6.1	1495
After mech.	37/16	32	344	131/72	96	7.4	1030
After amino.	18/5.5	10.8	116	229/78	94.3	7.4	1019
A.T. M 40							
Before med.	21/10	15.6	230.8	130/83	106	5.4	1568
After mech.	24/13.5	23.2		112/91	91		
After amino.	10/5	7.6	58.2	126/87	102	10.4	780
After amino.	17/4.4	7.5	131	118/83	88	4.5	1542
E.W. F 24							
Before med.	21/9	14.7	238.6	130/70	96	4.8	1574
After mech.	28/17	23.5	460	105/60	76	4.0	1488
After amino.	21/7.7	19.3	292	143/101	121	5.2	1831
After adren.	22/8	11.6	220	145/95	115	4.2	2188

Average changes with asthmatic attack: Systolic 23.4 per cent, Diastolic 38.2 per cent.

Adrenalin, on the other hand, reduces bronchiolar spasm, which, theoretically, should cause a fall in pulmonary arterial pressure, but, because it constricts the pulmonary arterioles, the pressure in the pulmonary artery remains elevated. This action, however, is brief, and the pulmonary artery pressure soon returns to normal.

During a moderate or severe attack of bronchial asthma the pulmonary arterial pressure is elevated. In our 10 cases the average increase in the systolic pressure was 23.9 per cent. Although the cardiac output is difficult to measure during asthmatic attacks, our data would tend to show that it is diminished.

It has been shown that aminophyllin and adrenalin increase cardiac output and that adrenalin increases it more than aminophyllin. Both drugs[6] may reduce bronchiolar spasm, but aminophyllin lowers the pulmonary arterial pressure, whereas, adrenalin does not during its usual period of action (5 to 8 minutes).

Our data indicates that there is a direct nervous or humoral control of the pulmonary circulation, but at the moment it is impossible to tell which it is. It seems likely that the elevation in pulmonary arterial pressure during an asthmatic attack is not due entirely to alterations in intrathoracic pressure (Figure 4). Note the marked fall in pulmonary arterial pressure at the beginning of inspiration. These observations suggest that the elevation of pulmonary arterial pressure in asthma is initiated by an

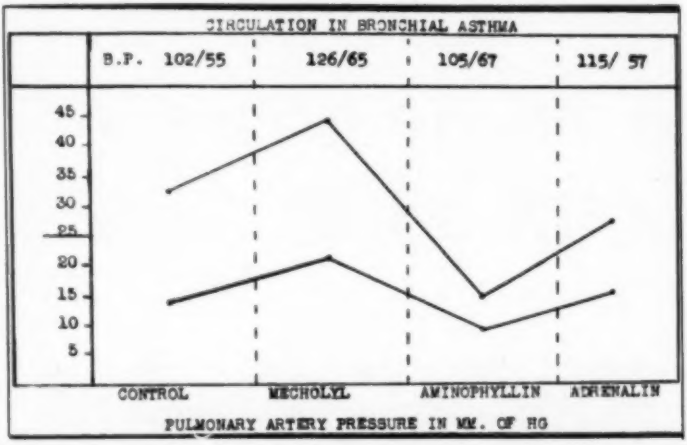

FIGURE 3: Is a graph which shows a typical response of the pulmonary arterial pressure in a patient with bronchial asthma. The asthmatic attack was introduced by giving mecholyl. Note the rise in pulmonary arterial pressure. With the administration of aminophyllin, the pressure fell to below the control level. Adrenalin was administered after the aminophyllin. Note the rise in pulmonary arterial pressure.

increase in alveolar pressure from bronchial constriction and alveolar swelling. Transmission of this pressure to the pulmonary capillaries and pulmonary arterioles brings about an increase in peripheral resistance.

Giving aminophyllin during an asthmatic attack caused the pulmonary arterial pressure to fall below the normal for that when the patient was not having asthma. This can be explained as follows: aminophyllin relieves the bronchiolar spasm, and this lowers the increased pressure in the alveolar sacs. As a result, peripheral resistance diminishes, and the pulmonary arterial pressure returns to normal. Aminophyllin has been shown to have a direct dilating effect on the pulmonary arterioles of animals. This

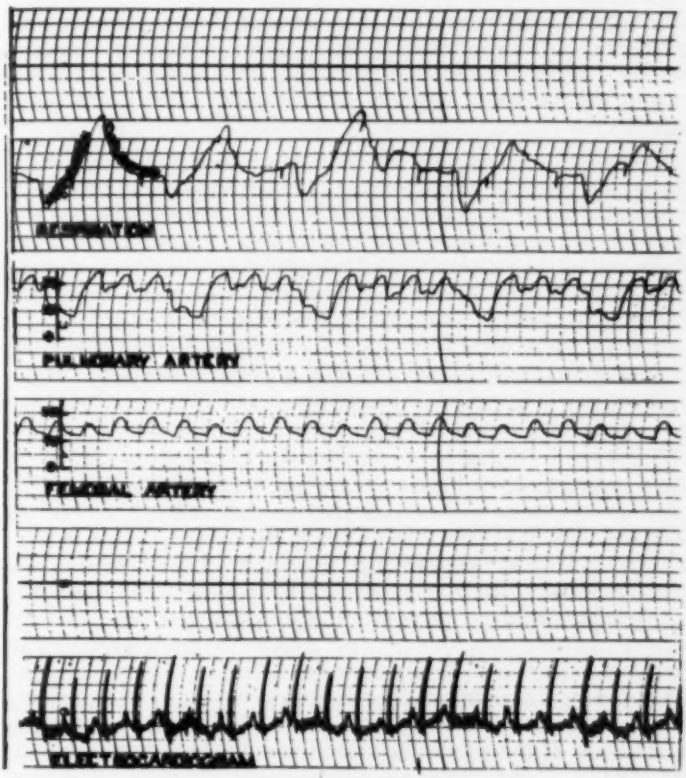

FIGURE 4: Is a tracing showing the changes in pulmonary arterial pressure during inspiration and expiration in a patient during a mild attack of bronchial asthma.

could account for the effect of the pulmonary arterial pressure.

With adrenalin the opposite effect is obtained. Adrenalin also causes relaxation of the bronchiolar muscle, but it has a direct constricting action on the pulmonary arterioles for a brief period. This tends to maintain the elevated pulmonary arterial pressure during the action of adrenalin. As the adrenalin effect wanes, the pulmonary arterial pressure approaches normal.

Wiggers,[7] in summarizing the nervous control of the pulmonary vessels, states that, "owing to the feeble responses obtained by nervous stimulation most physiologists have been inclined to question their importance in the regulation of the pulmonary circulation." He believes that "a critical review of all the experimental evidence leaves no doubt as to the existence of vaso-motor nerves to the pulmonary vessels in mammals and further strongly indicates that vaso-constriction impulses travel chiefly over the sympathetic system. Evidence as to the course or even the existence of vaso-dilator fibers, however, remains less certain and rather confusing."

Cournand,[8] who recently reviewed this aspect of the pulmonary circulation stated, "the demonstration of vaso-motor effects in the pulmonary circulation of man is still wanting. At best it may be conceeded that if any vaso-motor activity exists under normal physiological conditions, it is superseded by the much more potent mechanical factor regulating pulmonary blood flow. In contradistinction to the systemic circulation where variations in peripheral resistance serve to regulate flow to various organs according to their needs, all parts of the pulmonary vascular bed and the alveolar spaces are equal in function, hence there is little cause for a regulation mechanism of blood distribution under normal conditions."

Our data suggest that there is a direct action on the pulmonary arterioles. It is mediated through the sympathetic, on the one hand, by adrenalin, which causes vaso-constriction and maintains pulmonary arterial pressure, and, on the other hand, through the parasympathetic, by aminophyllin, which causes vaso-dilatation and lowers pulmonary arterial pressure. Whether this action of these drugs be humoral or nervous cannot be stated at this time, but, be that as it may, a direct regulating action of the pulmonary circulation is shown. Recent work of Hickam, et al.,[9] and of Reilly, et al.,[10] also tends to support this thesis. Hickam showed that constriction of the pulmonary arterioles occurred during anxiety and emotion. Reilly showed anoxemia will raise pulmonary arterial pressure. Reducing the oxygen content of the inspired air to 10 per cent caused significant rises in pulmonary arterial pressure.

The Pulmonary Circulation in Cases of Cor Pulmonale

In 1940, Scott and Garvin, in a paper entitled "Cor Pulmonale; Observations in 50 Autopsy Cases,"[11] stated that, "as we have no means of measuring the pulmonary blood pressure in man, the only available indez of right-sided heart strain is hypertrophy and dilatation of the right ventricle." Since Bloomfield's[19] work, we are able to measure pulmonary artery pressure in man with no difficulty, and we have now studied 36 cases of cor pulmonale.

Pulmonary arterial pressures were averaged for an entire phase of respiration because great variations occur between inspiration and expiration. The pressure increases on expiration and decreases on inspiration. Both pulmonary and systemic resistances were calculated by Aperia's formula.

The 36 cases can be broken down as follows: Table I summarizes the data on the 15 patients who had no congestive failure and were not digitalized. The average systolic pressure in the pulmonary artery was 50 mm. Hg., and the average diastolic pressure was 22.4 mm. Hg. The average heart rate was 94, and the average cardiac index, 3.38 liters/minute. Table I-A summarizes the clinical observations in these cases.

Table II summarizes the data on 14 patients who were digitalized and had no congestive failure. The average pulmonary artery systolic pressure was 60 mm. Hg., and the average diastolic pressure, 25 mm. Hg. The average heart rate was 83, and the average cardiac index was 3.21 liters/minute. Table II-A summarizes the clinical data in these cases.

Table III summarizes the data on three patients who had congestive heart failure and received no digitalis. The average pulmonary artery systolic pressure was 66 mm. Hg., and the average diastolic pressure was 39 mm. Hg. The average heart rate was 100, and the cardiac index was 4.31 liters/minute. Table 3-A summarizes the clinical data in these cases.

Table IV summarizes the data on four patients who had congestive heart failure in spite of digitalization. The average pulmonary artery systolic pressure was 67 mm. Hg., and the average cardiax index was 3.8 liters/minute. Table IV-A summarizes the clinical data in these cases.

The effect of rapid digitalization in cases of cor pulmonale with congestive heart failure is under study. Data are presented in Table V on four patients. Three who did not have congestive failure were given 1.6 mg. of Cedilanid intravenously. The cardiac output and pressures were recorded after one hour in one case and in three to five days in two others. No significant change in cardiac output occurred. This agrees with our observation on

TABLE I: Summary of the hemodynamics as found in 15 patients with cor pulmonale without congestive heart failure. Note the significant increase in pulmonary arterial pressure and pulmonary artery resistance.

Pt.	Age	Cardiac Index	H.R.	FEMORAL ARTERY S/D mm. Hg	FEMORAL ARTERY Mean mm. Hg	Systemic Resistance dynes/cm5/second	PULM. ARTERY S/D mm. Hg	PULM. ARTERY Mean mm. Hg	Pulmonary Resistance dynes/cm5/second	RIGHT AURICLE S/D mm. Hg	RIGHT AURICLE Mean mm. Hg
J.W.	63	4240	90	127/70	100.5	1612	41/27	31.4	504	6/3	2.5
J.M.	63	3380	120	112/73	102	2381	41/23	31.7	861	3/.2	— .67
A.M.	74	3240	90	85/50	64.5	1098	43/18	29.4	500	1/—4	—1.2
C.M.	54	3780	120	141/95	114	1562	66/27	38	529	1/—7	—3.2
J.A.	61	3760	100	126/70	88	1338	86/25	52	802	5/—3	.2
G.G.	69	4540	78	130/60	95	991	41/16	28	292	4/—1	— .4
L.G.	64	2460	107	150/94	116	3771	43/26	33.2	1078		—2.47
R.L.	52	3370	111	162/103	125	2960	45/26	33.4	820	6/2	4.0
J.G.	65	4540	80	175/100	94	948	45/21	30.6	308	4/—3	.7
J.D.	75	—	83	99/57	76	—	48/15	40.2		.5/—2	—1
J.S.	58	2190	80	114/60	77	2850	37/17	25	928	3/.3	1.0
M.R.	63	1680	82	115/58	86	4090	71/30	50	238	4/1	2.0
V.W.	60	4090	110	120/63	87	1720	55/23	38	746	6/—2	2.0
S.W.	49	2520	80	125/68	90	2860	42/15	26.6	844	1/—7	—3
B.S.	71	3620	88	133/76	97	2158	50/27	35.2	784	5/—2	.3
Average		3380	94	128/73	94	2160	50/22	34.8	660	3/—2	.037

TABLE I-A: Summary of the clinical and laboratory findings in the 15 patients with cor pulmonale without congestive failure.

Pt.	V. C. Per cent	Rbc.	Hgb. Gms.	Loud P2 $P_2 > A_2$	Chronic Emphysema	Lung Disease	Roentgenogram	Electrocardiogram
J.W.	30	5.8	14	$A_2 > P_2$	Yes		P. A. prominent.	Large P waves 2, 3. Right axis.
J.M.	28	4.6	13.4	$P_2 > A_2$	No		P. A. prominent.	Large P waves 2, 3. Right axis.
A.M.	40	3.06	13	$A_2 > P_2$	Yes	Bronchiectasis.	P. A. prominent.	Large P waves 2, 3. Right axis.
C.M.	25	4.06	8	$A_2 > P_2$	Yes		P. A. slightly prominent.	Normal.
J.A.	54	4.15	12	$A_2 = P_2$	Yes	Bronchogenic Ca.	Large P. A. and R. V.	Large P waves 2, 3. Right axis.
G.G.	27	3.96	14.5	$P_2 > A_2$	Yes		P. A. prominent. R. V. large.	Right ventricular hypertropny.
L.G.	46	4.47	13.5	$P_2 > A_2$	Yes	Pneumonitis right base.	P. A. prominent.	Large P waves 2, 3.
R.L.	40	5.1	15	$A_2 > P_2$	Yes	Minimal tuberculosis.	P. A. prominent. R. V. large.	Large P waves 2, 3.
J.G.	<50	5.34	14	$A_2 > P_2$	Yes	Possible pul. infarction.	Dense shadows mid lung field.	Large P wave 2. Right axis.
J.D.	23	3.6	11.5	$P_2 > A_2$	Yes	Bronchogenic Ca.	Large P. A. and R. V.	Large P waves 2, 3. Right axis.
J.S.	48	5.0	14	$P_2 > A_2$	Yes	Chronic bronchitis.	P. A. prominent.	Large P waves 2, 3.
M.R.	46	5.9	18	Loud P_2	Yes		Large P. A. and R. V.	Large P wave 2. Right axis.
V.W.	46	4.68	15	$P_2 > A_2$	Yes		P. A. prominent.	Large P waves 2, 3. Right axis.
S.W.	39	5.2	13	$A_2 = P_2$	No		P. A. prominent.	Large P waves 2, 3.
B.S.	54	4.9	16	$P_2 > A_2$	Yes	Silicosis.	P. A. prominent.	Large P waves 2, 3. Right axis.

TABLE II: Summary of the hemodynamics as found in 14 patients with cor pulmonale who were under the influence of digitalis but had no congestive heart failure at the time of study.

Pt.	Age	Cardiac Index, cc/min.	H.R.	FEMORAL ARTERY S/D mm. Hg	FEMORAL ARTERY Mean mm. Hg	Systemic Resistance dynes/cm5/second	PULM. ARTERY S/D mm. Hg	PULM. ARTERY Mean mm. Hg	Pulmonary Resistance dynes/cm5/second	RIGHT AURICLE S/D mm. Hg	RIGHT AURICLE Mean mm. Hg
A.M.	74	2290	100	122/65	88	2038	55/17	36.6	840	3/−2	.65
J.S.	60	1320	50	137/55	89	1101	61/23	36.1	804	5/−2	2.4
B.G.	24	4320	100	93/63	79	1271	57/29	38	604	−1/−8	−3.1
H.A.	59	5130	80	125/77	96.3	853	55/27	37.1	523	5/−2	2.2
C.B.	56	4410	80	95/63	73	1323	32/22	27	489	2/−1	− .05
G.G.	69	3500	80	125/70	96	1278	37/17	23.8	316	3/−1	3.1
J.K.	66	4270	90	110/65	75	887	66/36	47.4	516	5/2	3.3
H.J.	59	3540	78	98/60	77.4	1738	85/27	65	1467	8/3	6.2
F.J.	63	2980	100	103/59	89	2027	52/21	33	618	−2/−7	−5.2
S.B.	60	3010	84	135/73	94	1715	53/23	37	675	4/.5	2.1
J.B.	36	4000	84	125/84	106	1652	67/27	45	704	11/−3	4.0
R.K.	37	3440	92	101/59	72	2370	73/29	48.3	1130	3/−2	1.0
J.S.	76	1300	70	130/57	83	5455	75/25	53.5	339	6/2.5	4.0
L.B.	49	1320	80	142/79	103.3	6250	71/31	46.9	285		1.5
Average		3210	83	117/66	87	2140	60/25	41	670	4/−1	1.58

TABLE II-A: Summary of the clinical and laboratory findings in the 14 patients with cor pulmonale who were taking digitalis but had no signs of congestive heart failure.

Pt.	V. C. Per cent	Rbc.	Hgb. Gms.	Loud P2 $P_2 > A_2$	Chronic Emphysema	Lung Disease	Roentgenogram	Electrocardiogram
A.M.	40	4.0	11.5	$A_2 > P_2$	Yes	Bronchiectasis.	P. A. prominent.	Large P waves 2, 3. Right axis.
J.S.	<50					Silicosis.	P. A. prominent. R. V. large.	Normal.
B.G.	39	5.8	14.0	$P_2 > A_2$		Tuberculosis. Thoracoplasty.	P. A. prominent.	Large, notched P waves 1, 2, 3. Rt. axis.
H.A.	48	4.0	13.5	$P_2 = A_2$	Yes		P. A. prominent.	Large P waves 2, 3.
C.B.	45	4.0	14	$P_2 > A_2$	Yes		P. A. prominent.	Large P waves 2, 3. Right axis.
G.G.	23	5.4	13.3	$P_2 > A_2$	Yes		P. A. prominent. R. V. large.	Right ventricular hypertrophy.
J.K.	29	5.6	16.4	$P_2 > A_2$	Yes		Large P. A. and R. V.	Large P waves 2, 3. Right axis.
H.J.	<50	6.9	15		Yes		Large P. A.	Large P waves 2, 3. Right axis.
F.J.	42	5.3	14.6	$P_2 > A_2$	Yes		Large P. A. and R. V.	Large P waves 2, 3. Right axis.
S.B.	<50	6.5	17	$P_2 = A_2$	Yes		Large P. A.	Large P waves 2, 3. Right axis.
J.B.	25	3.35	14	$A_2 > P_2$	Yes	Bronchial asthma.	Prominent P. A.	Large P waves 2, 3. Right axis.
R.K.	64	6.1	17.3	$P_2 > A_2$	Yes		Large P. A. and R. V.	Large P waves 2, 3. Right axis. Prominent R in V leads.
J.S.	63	5.1	14	$A_2 > P_2$	Yes		P. A. prominent.	Large P waves 2, 3. Right axis. QRS 0.10 second.
L.B.	34			$P_2 > A_2$	Yes		Large P. A. and R. V.	Large P waves 2, 3. Right axis.

TABLE III: Summary of the hemodynamics as found in three patients with cor pulmonale and congestive heart failure without the digitalis therapy. The right ventricle diastolic pressure was also elevated in these cases.

Pt.	Age	Cardiac Index, cc/min.	H.R.	FEMORAL ARTERY S/D mm. Hg	FEMORAL ARTERY Mean mm. Hg	Systemic Resistance dynes/cm5/second	PULM. ARTERY S/D mm. Hg	PULM. ARTERY Mean mm. Hg	Pulmonary Resistance dynes/cm5/second	RIGHT AURICLE S/D mm. Hg	RIGHT AURICLE Mean mm. Hg
M.S.	23	5120	120	119/86	100	982	100/65	77	750	21/14	17.5
J.V.	57	4770	80	122/94	106	1150	37/20	25.8	246	11/2	7.0
B.N.	26	3060	100	102/75	87	1035	60/33	44	545	18/7	11.9
Average		4316	100	114/85	98	1072	66/39	48.9	514	17/7.6	12.1

TABLE III-A: Summary of the clinical and laboratory findings in the three patients with cor pulmonale with congestive heart failure and no digitalis.

Pt.	V. C. Per cent	Rbc.	Hgb. Gms.	Loud P2 $P_2 > A_2$	Chronic Emphysema	Lung Disease	Roentgenogram	Electrocardiogram
M.S.	34		15.8	$A_2 > P_2$	Yes	Tuberculosis.	Distorted, thoracoplasty.	Large P waves 1, 2. Right axis.
J.V.	>50	5.25	15	$A_2 > P_2$	Yes		P. A. not large.	Right axis.
B.N.	500 cc.	5.2	11.7	$P_2 > A_2$	No	Ac. Infection.	P. A. prominent.	Large P waves 2, 3. Right axis.

TABLE IV: Summary of the hemodynamics in four patients with cor pulmonale and congestive heart failure, who had in addition been taking therapeutic amounts of digitalis.

Pt.	Age	Cardiac Index, cc/min.	H.R.	FEMORAL ARTERY S/D mm. Hg	FEMORAL ARTERY Mean mm. Hg	Systemic Resistance dynes/cm5/second	PULM. ARTERY S/D mm. Hg	PULM. ARTERY Mean mm. Hg	Pulmonary Resistance dynes/cm5/second	RIGHT AURICLE S/D mm. Hg	RIGHT AURICLE Mean mm. Hg
C.K.	60	6074	80	123/75	93	2041	38/21	29.8	680	10/6	9.2
W.R.	58	3840	111	109/77	98	2235	75/35	50.5	1140	14/7	10.5
M.V.	33	3460	110	96/67	75	1278	90/52	67.7	1136	14/2	9.6
J.R.	49	2152	90	116/78	91.5	3390	64/34	44.5	1648	15/7	10.0
Average		3881	98	111/74	89.3	2238	67/35	48.1	1151	13/5	9.8

TABLE IV-A: Summary of the clinical and laboratory findings in the four patients as described in Table IV.

Pt.	V. C. Per cent	Rbc.	Hgb. Gms.	Loud P2 P2>A2	Chronic Emphysema	Lung Disease	Roentgenogram	Electrocardiogram
C.K.	50				Yes		P. A. not large.	Low voltage all leads.
W.R.	50	4.3	13.3	$P_2>A_2$	Yes	Bronchial asthma.	P. A. slightly prominent.	Large P waves 2, 3. Right axis deviation.
M.V.	400 cc.	6.7	15	Loud P_2		Tuberculosis. Thoracoplasty.	P. A. prominent.	Large P waves 2, 3. Right axis deviation.
J.R.	37	6.21	15	Loud P_2	Yes		P. A. prominent. Large R. V.	Large P waves 2, 3. Right axis deviation.

TABLE V: This chart summarizes the hemodynamics in four patients with cor pulmonale who were digitalized rapidly.

Patient	Drug		Base Line	3/4 to 1-3/4 Hours After	3 to 5 Days After
G.G.	Cedilanid	P. A.			
	No cong.	S/D	38/17 mm. Hg	35/19 mm. Hg	
	failure	Mean	26	26.4	
		R. V.			
		S/D		36.2/0 mm. Hg	
		F. A.			
		S/D	144/102 mm. Hg	150/85 mm. Hg	
		Mean	119	115	
		H. R.	77	94	
		C. O.	7,640 cc./min.	7,216 cc./min.	
W.R.	Ouabain	P. A.			
	Cong.	S/D	76/35 mm. Hg	68/31 mm. Hg	
	failure	Mean	50.5	43.3	
		R. V.			
		S/D	75/11 mm. Hg	62/7.5 mm. Hg	
		F. A.			
		S/D	110/77 mm. Hg	130/68 mm. Hg	
		Mean	93.8	89.5	
		H. R.	111	90	
		C. O.	6,540 cc./min.	7,810 cc./min.	
J.S.	Cedilanid	P. A.			
	No cong.	S/D	37/17 mm. Hg		42/17 mm. Hg
	failure	Mean	25		29
		R. V.			
		S/D	36/.75 mm. Hg		41/−1.7 mm. Hg
		F. A.			
		S/D	114/61 mm. Hg		124/70 mm. Hg
		Mean	77		82
		H. R.	62		58
		C. O.	3,405 cc./min.		3,390 cc./min.
S.W.	Cedilanid	P. A.			
	No cong.	S/D	42/15 mm. Hg		40/18 mm. Hg
	failure	Mean	28		29
		R. V.			
		S/D	33/−15.5 mm. Hg		33.6/−7.5 mm. Hg
		F. A.			
		S/D	125/68 mm. Hg		119/69 mm. Hg
		Mean	96		94
		H. R.	80		80
		C. O.	3,850 cc./min.		3,420 cc./min.

patients who did not have congestive failure and had been rapidly digitalized.[13] We feel as do others,[14,15] that a 15 per cent change in cardiac output must take place before the results can be accepted as significant. One patient with congestive heart failure was given 0.5 mg. of ouabain intravenously. The cardiac output increased by 1270 cc./minute, or a 19 per cent increase in 45 minutes. The pulmonary arterial pressure did not rise.

This work is continuing, and we expect to collect data on patients with congestive heart failure who have received cedalanid intravenously for reports[16,17] vary as to the action of digitalis.

One case of acute cor pulmonale deserves special comment. The patient was a 26-year-old Negro who had a history of cough, sputum, and fever for three weeks. The heart showed right ventricular and conus activity and the pulmonic second sound was louder than the aortic second. There was right axis deviation in the ECG. Roentgenologic study revealed enlargement of the right ventricle and pulmonary artery. Numerous small nodules were scattered throughout the chest. No tubercle bacilli or fungi were found in the sputum. With antibiotic therapy the process resolved slowly, and the congestive heart failure which was present at first had disappeared one month later. Figure 5 summarizes the data in this case and Figure 6 shows the roentgenograms of the chest before and after treatment.

All of the patients with cor pulmonale in this series had a significant elevation in the pulmonary resistance. McMichael states

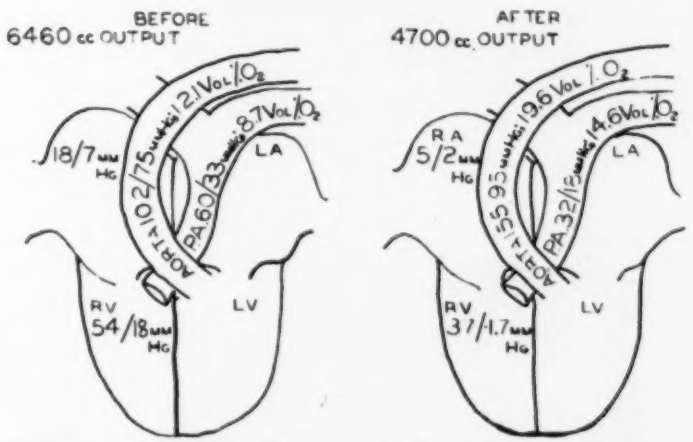

FIGURE 5: Our diagrams which summarize the hemodynamics in a patient with cor pulmonale due to acute infection studied during his congestive cardiac failure and again after there was no congestive failure present. See text for details.

FIGURE 6: Our x-ray films of the chest on the patient with cor pulmonale, due to an acute nodular pneumonitis. In the film on the left taken at the time the patient had congestive cardiac failure, note the nodulation present in the lung fields and the enlarged heart with a prominent pulmonary artery. In the film on the right taken after the infection and congestive failure had disappeared, note the diminution in size of the heart and the clear lung fields.

FIGURE 7: This table is a summary of the pulmonary capillary pressures in four patients with cor pulmonale.

Pt.	Sex	Age	Cardiac Index	Rate	P.A. S/D	P.A. Mean	Systemic Resistance dynes/cm5/sec.	P.A. S/D	P.A. Mean	Pulmonary Resistance	P.C. Mean mm. Hg
R.L.	M	52	3,370 cc.	111	162/103	125	2961	49/26	34.6	821	8.0
B.S.	M	71	3,620 cc.	88	133/76	97	2142	50/26	35.2	778	3.0
C.B.	M	39	3,825 cc.	107	210/125	145	3015	34/21	24.4	509	3.5
L.G.	M	64	2,460 cc.	107	150/94	116	3771	43/26	33.2	1078	5.7

FIGURE 7A: Summary of the clinical findings in the four patients in which pulmonary capillary pressures were measured.

Pt.	Age	Sex	V. C Pct.	Pct. 0_2 Sat.	A-V Diff.	Electrocardiogram	Roentgenology	Physical Findings
L.R.	52	M	40	67	4.5	NSR Intermediate heart	P. A. prominent R. V. & L. V. enlarged	$A_2 > P_2$
B.S.	71	M	54	87	5.3	Vertical heart Right axis		$P_2 > A_2$ No murmur
C.B.	39	M	34	91	4.1	Vertical heart Right axis Peaked P_2 & P_3	Distorted Old thoracoplasty	$P_2 > A_2$ No murmur
L.G.	64	M	46	81	5.4	NSR Vertical heart Large P waves	Both P. A.'s enlarged	Slight enlargement $P_2 > A_2$

FIGURE 8: Summary of hemodynamic studies in a patient with pulmonary arteriolar sclerosis who was given aminophyllin.

Cardiac Index	Rate	P. A. S/D	P. A. Mean	Pulmonary Resistance dynes/cm.5/sec.	P. A. S/D	P. A. Mean	Systemic Resistance dynes/cm.5/sec.
Before Aminophyllin: 2560 cc.	84	96/52	67	2095	107/71	82.5	2542
After Aminophyllin (10 min.): 2340 cc.	90	102/57	70.5	2518	79/45	58.5	1929

TABLE VI: This chart summarizes the findings in a group of 29 patients who received amminophyllin intravenously.

		BASELINE				Max.	AFTER AMINOPHYLLIN			
Name	Diagnosis	P.A. S/D	Mean	F.A. S/D	Mean	Time Min.	P.A. S/D	Mean	F.A. S/D	Mean
J.D.	Cor pul.	49/15	40.2	105/63	76	10	37/13	22.8	96/61	73
G.G.	Cor pul.	41/16	28	130/67	94.5	10	30/14	21.4	147/85	114
J.G.	Cor pul.	45/21	30.6	175/99	94	3	36/7	20.5	160/70	107
A.M.	Cor pul.	44/19	29.4	95/50	64.5	30	34/18	24.5	106/66	81
L.C.	Cor pul.	63/25	40.3	117/61	91	1	45/20	31.1	115/55	72
O.J.	Asthma	32/20	36	127/75	100	5	21/15	18		
L.J.	Asthma	24/10	18.1	175/99	130	5	19/10	16.6	190/112	125
E.M.	Asthma	29/10	19.7	142/96	116	15	19/6	12.2	153/99	120
P.S.	Asthma	25/13	19	127/70	95	6	19/10	14	127/87	97
R.S.	Asthma	32/14	24.4	102/55	78	10	15/8	14.6	105/67	84
A.T.	Asthma	21/10	15.6	130/83	106	13	10/5	7.6	126/88	
E.T.	Asthma	24/12		115/85		1	14/10		110/85	
J.W.	Asthma	25/9		150/99		32	11/4		122/84	
R.W.	Asthma	25/9				12	15/6			
F.W.	Asthma	26/11	17.8	146/74	111	6	18/3	13.4	129/78	94
E.W.	Asthma	19/5		98/56		35	14/4		110/70	
E.W.	Asthma	21/9	14.7	130/70	96	25	19/6	11.8	143/99	121
P.Y.	Asthma	22/12		114/82		1	12/4		95/75	
L.B.	Asthma	35/11	29	142/80	105	15	10/3	7.6	94/66	77
R.B.	H.C.V.D.	60/35	45	125/90	101	5	33/21	27	125/100	112
F.N.	H.C.V.D.	31/15	21.4	195/85	117	30	18/12	17.4	210/105	150
S.V.	No H.D.	25/12		140/98		38	11/4		112/77	
S.C.	Pericard.	25/10	16.9	115/60	85	5	19/7	13.5	105/65	82
F.K.	Broncho. Ca.	52/21		132/62		15	28/12		123/69	
L.B.	Cor pul.	72/33	46.9	142/79	103	5	46/21	37.2	132/94	
L.G.	Cor pul.	44/20	33.2	150/94	116	15	22/17	21.1		
R.L.	Cor pul.	46/26	33.4	122/80	98	10	38/23	30.4	130/80	100
B.S.	Cor pul.	55/28	40.0	133/76	89	12	41/18	30.0		
R.K.	Cor pul.	73/28	50.8	101/59	80	28	46/16	30.8	100/60	80
Average		37/20	29.7	132/78	99	14	24/9	20.1	123/83	101

and both Epinger and Dexter[12] have shown, that this elevation is caused by pulmonary arteriolar constriction. They found that the pulmonary capillary pressure of patients with cor pulmonale was normal. This theory is furthered by our observation that pulmonary arterial pressure is lowered by giving aminophyllin. We have measured pulmonary capillary pressure by the method of Dexter in four cases of cor pulmonale and have found that it is normal (Figure 7). Figure 7-A summarizes the clinical findings in these four cases.

Our results tend to substantiate those of J. Lenegre,[18] that cor pulmonale raises pulmonary arterial pressure, and do not support the conclusions of Bloomfield,[1] Cournand,[19] and Borden, et al.[20] Borden and his co-workers reported four cases of failure, with no significant difference of pressure between those with cor pulmonale, and those with chronic emphysema without cardiac failure.

The pulmonary diastolic pressure of patients with chronic pulmonary emphysema is 100 to 600 per cent above normal, and this reflects an increase in pulmonary arterial resistance. The burden on the left side of the heart becomes great if the diastolic pressure is elevated only 25 per cent. In some cases of emphysema it is remarkable that the right side of the heart is able to carry the extra load as long as it does. We would like to take exception to the work of Muller, as quoted by McMichael,[21] which states that the right ventricle has little compensatory power.

Action of Drugs on Pulmonary Circulation

We have studied the effect of papaverine on six patients with elevated pulmonary arterial pressure and have been unable to modify the pressure significantly. Standard textbooks list papaverine as the drug of choice in the treatment of pulmonary embolism, but it seems to have little dilating effect on the pulmonary arterioles.

However, we have observed that aminophyllin lowers elevated pulmonary arterial pressure consistently. Table VI summarizes the data in 29 cases. The average lowering of the systolic pressure was 35 per cent, and the average lowering of the diastolic pressure was 55 per cent. In only one case were we unable to lower the pressure. This patient had pulmonary arteriolar sclerosis, and his pressure actually rose, as shown in Figure 8. This is in keeping with the concept of the dynamic action of the pulmonary circulation, because, in this case, the arterioles could no longer dilate under any circumstances. It appears that the drug of choice for patients with pulmonary embolism is aminophyllin, administered intravenously.

Pneumonectomy

Cournand[22] studied pulmonary hemodynamics before and after pneumonectomy in man, but he did not observe the changes which occur during the actual operative procedure. He found no significant alteration in the pulmonary arterial pressure after pneumonectomy.

We have studied pulmonary hemodynamics by the technique of catheterization of the right side of the hearts of six patients who were undergoing pneumonectomy, in one who was undergoing lobectomy, and in one during exploratory thoracotomy. During the operation a sudden burden might be thrown on the vascular bed of the remaining lung at the time of ligation of the opposite pulmonary artery.

A catheter was placed in the pulmonary artery opposite to the one to be ligated approximately one hour before the induction of anesthesia. The pulmonary arterial pressure was measured then and at 15-minute intervals throughout the entire procedure, including the immediate period of ligation and after closure of the chest. By means of the Sanborn Cardioscan, the electrocardiogram was visable throughout the entire procedure.

In two cases in which the lesions were not resectable the pulmonary arterial pressure measurements were obtained after temporary ligation of one pulmonary artery.

During the induction of anesthesia both the systolic and diastolic

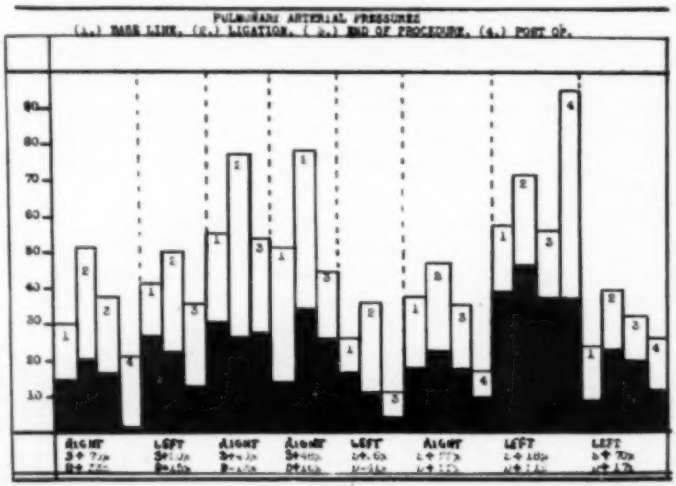

FIGURE 9: The block graph summarizes the data on eight patients who had a ligation of either the right or left pulmonary artery.

pressure in the pulmonary artery rose, and, in some cases this continued throughout the preligation period. The increase in diastolic pressure was greater than in the systolic, averaging, in the former, 70 per cent, and, in the latter, 30 per cent.

Figure 9 summarizes the observations in eight cases. The change in systolic pressure after ligation ranged from 18 to 70 per cent; the average was 40 per cent. The increase in diastolic pressure was from 16 to 33 per cent, except that in three cases a decrease from 13 to 41 per cent occurred. There was a greater change in pressure, as a rule, with the ligation of the right than with the left pulmonary artery.

In the graph the diastolic pressures are shown in the shaded area, and the systolic pressures in white. The dotted lines separate cases. The numbers above the blocks indicate: (1) the base-line pressures five to 10 minutes before ligation of the pulmonary artery, (2) the change at the time of ligation of the pulmonary artery, (3) which, on the average, was two hours after the ligation of the pulmonary artery, and (4) the postoperative measurements, which were made two to six weeks later.

Case 7 deserves special comment. This 50-year-old man with emphysema and carcinoma of the right upper lobe of the lung, developed congestive heart failure after operation, and was digitalized. The pulmonary arterial pressure and the pulmonary capillary

FIGURE 10: This chart summarizes the pre and post hemodynamic studies on a patient who after pneumonectomy developed congestive cardiac failure.

Case of F.K., Left Upper Lobectomy

	Pre-Operatively 2 Weeks	Post-Operatively 6 Weeks
Systemic Pressures, mm. Hg	132/62	120/62
Pulmonary Artery, mm. Hg	52/20	95/37
Right Auricle, Mean Pressure	5.7 mm. Hg	10.9 mm. Hg
Cardiac Index, cc./min.	4,500	5,776
Stroke Volume, cc.	117	110

Response to Aminophyllin 0.5 Gm. Intravenously

Pulmonary Artery, mm. Hg	Control 52/20 Maximal Response 15 min. 28/11	
Pulmonary Capillary Method of Dexter Mean Pressure		Control 27.4 Maximal Response 7 min. 17.5

TABLE VII: Summary of the clinical and hemodynamic studies in five patients with insufficiency of the pulmonary valve.

Patient Age Sex Diagnosis	Physical Findings	Fluoroscopy	E. C. G.	Pul. Artery Pressure and Mean	R. V. and P. A. Pressure	Cardiac Output cc/min.
H.J. 59 M Prob. cor. pul. Autopsy: Lues of pul. artery, Cor pulmonale	$P_2 > A_2$ Emphysema. Dist. neck veins. Marked conus Activity. Gr. iii pul. diast. m.	P. A. and conus large with active pulsations. R. V. enlarged.	Rt. axis deviation. Large P waves in L 1, 2, 3, aVr, aVf.	85/27.5 Mean 65	R. V. 87/9 F. A. 98/60	3,540
M.McD. 31 F Pulmonary arteriolar sclerosis	Polycythemia Cyanosis. Marked conus and R. V. activity. Gr. iii pul. diast. m.	Enlarged P. A. segment. Pulsating hilar vessels R. V. enlarged.	Rt. axis deviation.	96/52.5 Mean 67	F. A. 107/72	3,600
E.P. 46 M Rheum. heart disease	Ht. enlarged to lt. and rt. Bouts of pul. infarctions. Diast. m. heard loudest at pul. area.	Enlarged R. V. P. A. and L. A.	Large P 1, 2, aVr, aVf.	105/53 Mean 73.2	R. V. 106/10 F. A. 115/65	3,210
		Aminophyllin 0.5 Gm. Given I. V.				
L.B. 49 M Cor pulmonale	*Before* $P_2 > A_2$ Emphysema diast. m. at pul. area.	Rt. and lt. V. enlarged. P. A. large with prom. vasc. marking.	Rt. axis deviation. Large P 2, 3.	71.5/31 Mean 46.9	R. V. 56/4.3 F. A. 142/79	2,338
	After Pul. diast. m. markedly decreased.			46.3/21.2 Mean 37.3	R. V. 41.8/5	
L.G. 64 M Cor pulmonale	*Before* $P_2 > A_2$ Emphysema. Pul. diast. m. Increased R. V. activity.	Both pul. arteries enlarged and dance. P. A. seg. markedly enlarged.	N. S. R. Semi-vert. heart. Large P 1, 2, aVf.	43/25 Mean 33.2	Premature beats. Very irrit. V. F. A. 150/94	4,190
	After Pul. diast. m. markedly decreased.			21.3/17 Mean 21		

pressure, before and after operation, were significantly lowered by aminophyllin. Observations on this patient after operation indicate that a significant elevation in the pulmonary arterial pressure probably militates against pneumonectomy. Figure 10 summarizes this case.

The immediate rise in pulmonary arterial pressure which places a sudden load on the right ventricle may be responsible for deaths which sometime occur after ligation of the pulmonary artery.

We have found that if the pulmonary arterial pressure is elevated, whatever the cause, it may be significantly lowered by the administration of aminophyllin, and the effect of this drug on patients undergoing pneumonectomy or lobectomy is being investigated.

In one case a catheter was introduced into the pulmonary vein that was to be ligated, and then into the left auricle, where no significant change in pressure occurred during or immediately after ligation of the pulmonary artery and veins. This is shown diagramatically in Figure 11.

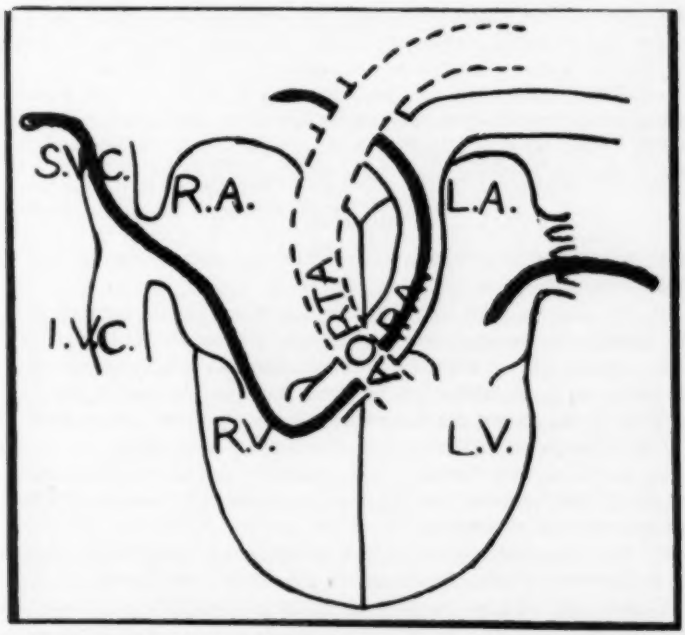

FIGURE 11: This is a schematic sketch showing the introduction of a catheter into the pulmonary vein at the time of operation.

Observations on the Hemodynamics in Cases of Insufficiency of the Pulmonic Valve

Five patients with typical physical signs of pulmonic insufficiency were studied by means of intracardiac catheterization, and it was found that the systolic pressure in the pulmonary artery averaged 80.5 mm. Hg., and the diastolic, 38 mm. Hg. Table VII summarizes the data in the five cases. In two cases the intravenous administration of 0.05 Gm. of aminophyllin caused the pulmonary arterial pressure to fall from 71/32 mm. Hg. to 50/20 mm. Hg., and from 43/25 mm. Hg. to 21/17 mm. Hg., respectively, and the intensity of the diastolic murmur of pulmonic insufficiency was markedly diminished in both cases.

Pulmonic insufficiency, like aortic insufficiency, results when normal leaflets cannot seal a dilated ring. Although both the systolic and diastolic pressures in the pulmonary artery were elevated, it is likely that the degree of incompetency of the pulmonic orifice was determined more by the level of the diastolic pressure, which was found to be relatively higher than the systolic.

Even in the presence of pulmonic insufficiency the diastolic pressure in the right ventricle was maintained nearly at zero when the patients had no congestive failure. Similarly, in cases of organic aortic insufficiency without failure we found that the diastolic pressure in the left ventricle was at or near zero.[23] Finally, pressure curves in cases of insufficiency of the pulmonic valve differ from those of classical organic aortic insufficiency in that the pulmonic curves do not show a rapid fall of pressure.

SUMMARY

1) A method of studying the pulmonary circulation in man is described.

2) All persons with moderate to severe bronchial asthma have an increase in pressure in the pulmonary artery.

A) Adrenalin relieves the bronchiolar spasm, but causes constriction of the pulmonary arterioles, thus maintaining pulmonary arterial pressure at the asthmatic level. However, this effect is rapidly dissipated, and the pressure returns to normal.

B) Aminophyllin relieves the bronchiolar spasm, but causes dilatation of the pulmonary arterioles, thus lowering pulmonary arterial pressure below normal.

C) Our observations indicate that these are vaso-motor or humoral reflexes which influence the pulmonary circulation in man.

3) Patients with cor pulmonale have a high pulmonary arterial pressure because the peripheral resistance in the lung is increased. The diastolic pressure is increased two to six fold.

A) The vascular bed is not fixed in cases of cor pulmonale, as is shown by the response to aminophyllin.

B) Patients with cor pulmonale and congestive heart failure respond favorably to digitalization.

C) Some patients with cor pulmonale had a low cardiac output; others had a high cardiac output with congestive heart failure.

D) The pulmonary capillary pressure is normal in cases of cor pulmonale. This indicates that the arteriolar bed is constricted.

4) In man, papaverine does not significantly alter pulmonary arterial pressure, but, aminophyllin consistently lowers it.

5) Patients undergoing pneumonectomy show an average increase of 40 per cent in the systolic pressure at the time of ligation of the pulmonary artery. The remaining pulmonary vascular bed, however, compensates for this added load in a period of ½ to 1½ hours.

A) Both the systolic and diastolic pressure in the pulmonary artery rise with the induction of anesthesia.

B) Catheterization of the pulmonary artery in man may prove useful in evaluating the risk of pneumonectomy.

6) Patients with insufficiency of the pulmonic valve have a high systolic and high diastolic pulmonary arterial pressure. Probably the most important cause of dilatation of the pulmonic ring is the high diastolic pressure.

I wish to acknowledge the technical assistance of Harvey Mendelsohn, M.D., and Arthur Adelman, M.D., for the work on pulmonary resection.

I am also deeply indebted to my two laboratory workers, Miss Gladys Heckman, R.N., and Miss Hanna Janouskvec, R.N., without whose understanding and help this work could not have been done.

RESUMEN

1) Se describe un método de estudio de la circulación pulmonar en el hombre.

2) Todas las personas con asma moderada o severa tienen un aumento de la presión en la arteria pulmonar.

A) La adrenalina alivia el espasmo bronquial, pero causa constricción de las arteriolas pulmonares manteniendo así la presión arterial pulmonar al nivel asmático. Sin embargo, este efecto se disipa bien pronto y la presión regresa a lo normal.

B) La aminofilina alivia el espasmo bronquial pero causa la dilatación de las arteriolas pulmonares bajando así la presión pulmonar abajo de lo normal.

C) Nuestras observaciones indican que estos son reflejos vasomotores o humorales que influyen sobre la circulación pulmonar en el hombre.

3) Los enfermos con corazón pulmonar tienen una alta presión

arterial pulmonar, porque la resistencia periférica en el pulmón aumenta. La presión diastólica está aumentada de dos a seis veces.

A) El lecho vascular no está fijo como lo muestra la respuesta a la aminofilina.

B) Los enfermos con corazón pulmonar y desfallecimiento cardiaco congestivo responden favorablemente a la digitalización.

C) Algunos enfermos con corazón pulmonar tienen un débito cardiaco bajo con desfallecimiento cardiaco congestivo.

D) La presión pulmonar capilar es normal en casos de cor pulmonar.

4) En el hombre la papaverina no altera de modo significante la presión arterial pulmonar, pero la aminofilina francamente la desciende.

5) Los enfermos que se someten a neumonectomía muestran un aumento medio de 40 por ciento de la presión sistólica en el momento de la ligadura de la arteria pulmonar. El lecho pulmonar restante sin embargo, compensa esta carga en un periodo de media a una hora y media.

A) Tanto la presión diastólica como la sistólica aumentan con la inducción de la anestesia.

B) La cateterización de la arteria pulmonar en el hombre es útil para valuar el riesgo de la neumonectomía.

6) Los enfermos con insuficiencia de la válvula pulmonar tienen una presión pulmonar sistólica y diastólica aumentadas. Probablemente la causa más importante de la dilatación del anillo pulmonar es la presión diastólica alta.

RESUME

1) Description d'une méthode permettant d'étudier la circulation pulmonaire chez l'homme.

2) Tous les individus atteints d'asthme discret ou grave ont une augmentation de la pression dans leurs artères pulmonaires.

A) L'adrénaline supprime le spasme bronchiolaire mais entraine une constriction des artérioles pulmonaires qui maintient la pression artérielle pulmonaire au même niveau qu'au cours de la crise d'asthme. Toutefois, cet effet se dissipe rapidement et la pression revient à la normale.

B) L'aminophylline supprime le spasme bronchiolaire mais entraine une dilatation des artérioles pulmonaires et ainsi abaisse au-dessous de la normale la pression de l'artère pulmonaire.

C) Les observations de l'auteur montrent que la circulation pulmonaire chez l'homme est influencée par des réflexes vasomoteurs ou humoraux.

3) Les malades atteints de "coeur pulmonaire" ont une pression de l'artère pulmonaire élevée due à l'accroissement de la résistance

périphérique dans le poumon. La pression diastolique est augmentée de deux à six fois.

A) L'état vasculaire n'est pas fixe dans les cas de coeur pulmonaire comme le montre la réponse à l'aminophylline.

B) Les malades atteints de coeur pulmonaire et d'insuffisance cardiaque congestive sont favorablement influencés par la digitaline.

C) Certains malades atteints de coeur pulmonaire ont un débit cardiaque bas, d'autres ont un débit cardiaque élevé avec une insuffisante cardiaque congestive.

D) La pression des capillaires pulmonaires est normale dans les cas de coeur pulmonaire. Ceci signifie qu'il existe une constriction artériolaire.

4) Chez l'homme la papavérine ne modifie pas nettement la pression de l'artère pulmonaire mais l'aminophylline l'abaisse de façon importante.

5) Les malades qui ont été l'objet d'une pneumonectomie ont une augmentation moyenne de 40% pour la pression systolique au moment de la ligature de l'artère pulmonaire, cependant les vaisseaux pulmonaires restants assurent une compensation de cette surcharge en un laps de temps durant de une demi-heure à une heure et demie.

A) Les pressions systolique et diastolique de l'artère pulmonaire augmentent avec le début de l'anesthésie.

B) La cathétérisme de l'artère pulmonaire chez l'homme peut donner des renseignements utiles sur le risque que peut faire courir une pneumonectomie.

6) Les malades atteints d'insuffisance pulmonaire ont une pression de l'artère pulmonaire élevée tant pour la systolique que pour la diastolique. Il est vraisemblable que la cause la plus importante de la dilatation de l'artère pulmonaire est la pression diastolique élevée.

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Bronchiogenic Carcinoma Masquerading as Other Diseases*

A Review of 200 Cases

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Early diagnosis of lung cancer has been thwarted by the camouflage of secondary pulmonary infection and lack of suspicion of malignancy until a delay of diagnosis eliminates any chance of surgical cure in the majority of lung cancer patients at the present time. This unfortunate situation seems especially to be deplored since lung cancer has gradually assumed its proper position among malignancies representing about 10 per cent of cancer deaths and ranking among the first three of the organs affected by cancer.[1-3] This same general incidence as reported elsewhere is noted in the vital statistics of Oregon, in that deaths from cancer of the lung and respiratory tract ranked second in 1948, being exceeded only by cancer of the intestinal tract. Comparing this with previous years, cancer of the respiratory tract ranked ninth in 1946 and fourth in 1947, indicating an apparent increase at least in the diagnosis of lung cancer.

The surgical treatment of lung cancer has almost reached its anatomical limits with the removal of involved chest wall, diaphragm and pericardium along with the affected lung. Earlier diagnosis and earlier distinction of lung cancer from its many disguises represents the only method of improving the present low operability rate and reducing the six months interval all too frequently found between onset of symptoms and surgical intervention.

A review of 200 patients with lung cancers seen in Portland since 1946 seems to compare reasonably well with other published data, although an operability rate as high as 35 per cent has been reported[2,4-6] in some series. Forty-three and one-half per cent of these 200 patients were inoperable on clinical examination alone, having obvious signs of extension of the cancer beyond the lung. The involvement of cervical nodes, trachea, recurrent laryngeal nerve, phrenic nerve and tumor cells in the pleural fluid were used as the chief criteria for inoperability. Another 32.5 per cent of these patients were found on exploration to have inoperable can-

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cers, even though a palliative pneumonectomy was done whenever it was technically possible to remove the adjacent involved structures. Four per cent refused operation. This provides an operability rate of only 20 per cent in this group, leaving much to be desired for improvement in diagnosis.

Although cancer of the lung can reproduce the roentgenological picture and symptoms of any other disease of the chest it can reproduce at least the symptoms of almost any other disease in the body. Rheumatic pain in the extremities, for instance, is one of presenting symptoms which supersedes, in importance to the patient at least, the "cigarette cough" which he tends to minimize. Arthralgia as a presenting symptom of bronchiogenic carcinoma was brought out by Berg[7] and represents the very earliest symptom in at least four of these 200 patients on whom colloidal gold injections, dental extractions and other forms of arthritic therapy had already been instituted. This does not include a considerable number of other patients who developed arthralgia during the course of their disease, but not as a presenting symptom.

The typical osteoarthropathies and clubbing of the nails were noted only in the slowly growing lesions and more advanced stages of the disease. Upper abdominal discomfort referred over the distribution of the lower intercostal nerves and associated with loss of weight and strength has represented the outstanding early symptom in at least 5 per cent of this series of lung cancers. These patients were not unnaturally considered to have abdominal diseases and it was only by the curiosity of an alert roentgenologist in fluoroscoping the chest during gastrointestinal series that the lung shadow was discovered. Needless to say, the patients whose lung cancers were explored only after an abdominal operation

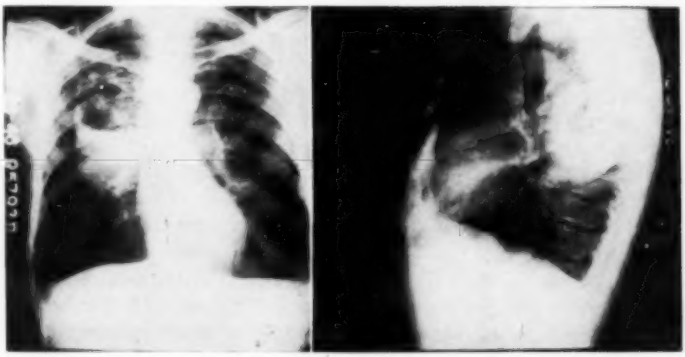

FIGURE 1: Roentgenogram suggests lung abscess but tumor cell found in bronchoscopic aspiration.

had failed to cure their symptoms presented far advanced lesions at the time of thoracotomy. Pancoast tumors with a Horner's syndrome as the first sign and these apical growths whose first symptoms come from cerebral metastases must be included in this group. Thus about 10 per cent of this series of lung cancers produced early symptoms which are entirely unrelated to the chest, leaving only 90 per cent to masquerade as chest diseases. Jaffe[1] presented a series of lung cancers in 25 per cent of which the first symptoms were entirely unrelated to the chest.

Virus pneumonia or segmental atelectasis and pneumonitis seems to represent one of the most frequent disguises of malignant bronchial obstruction. The marked similarity of both the symptoms and roentgenographic shadow during early stages make this a natural error; but, when "virus pneumonia" continues after a couple of weeks of conservative medical treatment a cancer should be suspected and investigated with a bronchoscope. If a cancer is present, one has a fairly good chance of observing and biopsying the tumor bronchoscopically in this type of browth which produces a central bronchial obstruction and atelectasis. It must be remembered, however, that the bronchoscope can visualize only about 40 per cent of the tracheobronchial tree and can be expected, therefore, to actually visualize only about 40 per cent of the bronchiogenic carcinomas in their early stages. With the aid of the flexible suction tubes additional tumors can be reached for aspira-

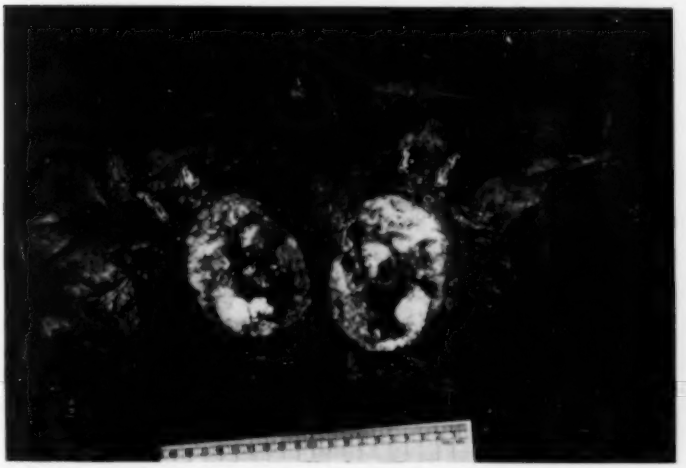

FIGURE 2: Pneumonectomy specimen of Figure 1 showing lung abscess cavity surrounded by necrotic cancer tissue.

tion biopsy of the bronchial secretions by the Papanicoleau method or some modification.

In this series positive bronchoscopic biopsies were obtained in only 45 per cent of the patients by a combination of the two methods. Large cancers with central necrosis and excavation resembling lung abscess on roentgenogram have provided some of the most satisfactory secretions for pathological examination. These tumors continually cast off cancer cells in such abundance that one may trace the complete cycle of mitosis, eliminating the element of uncertainty sometimes found in aspiration biopsies. It is quite probable that an increased number of positive aspiration biopsies could have been obtained by repeated bronchoscopies over a period of months, if some of these patients had been allowed to develop their cancers more extensively, but a number of them were explored on the basis of their history and roentgen pictures without waiting for a positive bronchoscopic biopsy.

This is the point to be stressed, that in order to reach the other 50 per cent of peripherally located lung cancers one must explore suspicious lesions without waiting for a positive bronchoscopic biopsy. An unexplained lung shadow should be treated in the same manner as a palpable mass in the breast or abdomen—by exploration and resection, the extent of the resection depending upon the type of pathology. The necessity for early exploration

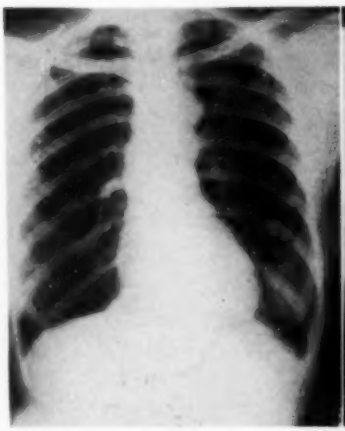

FIGURE 3

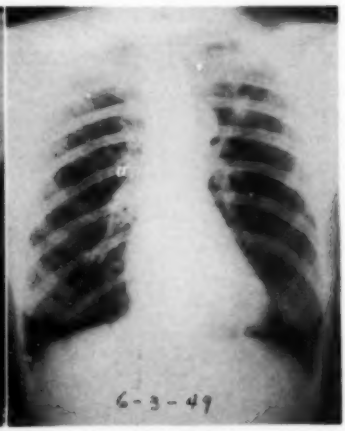

FIGURE 4

Figure 3: Suggestive "tuberculoma" found on routine roentgenogram. Patient asymptomatic and bronchoscopic examination negative, including pathology examination of aspirated bronchial secretions. — *Figure 4:* Same patient as Figure 3 nine months later. Bronchoscopy still negative but exploratory thoracotomy showed lung cancer with involved mediastinal nodes.

and resection of solitary nodules which appear like tuberculomas, inspissated lung abscesses and even mediastinal tumors should be apparent, since these lesions provide neither tubercle bacilli or tumor cells to establish a laboratory diagnosis. The instability of uncalcified tuberculomas or blocked cavities over one centimeter in diameter is notorious, making resection of such a solitary lesion desirable, even though it can be definitely established as tuberculous in origin. Even more notorious is the tendency for early peripheral bronchiogenic carcinomas and bronchial adenomas to simulate tuberculomas, only to become inoperable while being watched. Of 35 solitary peripheral lung shadows which came to resection during the past four years 67 per cent proved to be new growths of some type and only 32 per cent represented tuberculomas or pseudo tumors. Incidently, no lesion was seen on bronchoscopy in any one of these 35 patients and no tubercle bacilli were found in their sputum examinations.

The same necessity for exploration is present in atypical apical infiltrations which do not provide a sputum positive for tubercle bacilli. Apical lung carcinomas are notorious for their difficulty in early diagnosis, often presenting their first signs and symptoms in the neck or brain, and it is only by more explorations that such cancers can be discovered in time for resection. An even more difficult problem is presented by upper lobe cancers which are associated with active tuberculosis and a positive sputum, three of which are included in this series. The diagnosis was delayed in these patients by the disguise of the positive sputum, but two

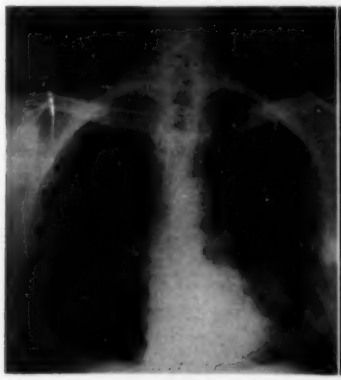

FIGURE 5

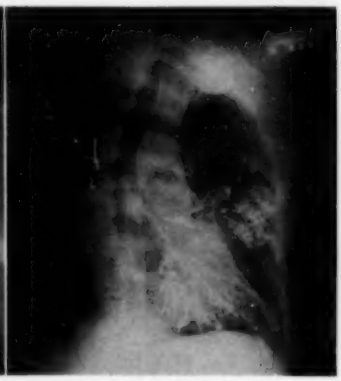

FIGURE 6

Figure 5: Left upper lobe cancer with symptoms referred along intercostal nerves to epigastriun. Bronchoscopy and pathological examination negative. *Figure 6:* Bronchogram on same patient as Figure 5 showing obstruction of lingular branch of left upper lobe bronchus beyond reach of bronchoscope.

tumors were resected and the third one abandoned due to far advanced contralateral tuberculosis.

Among the disguises of lung cancer one must mention pyogenic empyemas which concealed two cancers in this group until after the pus had been drained. Two other patients arrived with the diagnosis of aneurysm of the aorta due to transmitted pulsations. Fortunately, none in this group had the misleading diagnosis of a rare type of primary fungus infection proved by cultures and disproven only by finding cancer at autopsy.

SUMMARY

1) Deaths from lung cancer represent about 10 per cent of all cancer deaths, placing cancer of the respiratory tract second only to cancer of the intestinal tract.

2) Delayed diagnosis reduced the operability rate of this series of 200 patients to 20 per cent. Forty-three and five tenths per cent of these patients were inoperable on clinical examination alone and another 32.5 per cent were inoperable on exploration.

3) Presenting symptoms referred to the abdomen and extremities represented the most frequent extrapulmonary disguises to delay diagnosis. Virus pneumonia, lung abscess, tuberculomas and mediastinal tumors represented the most frequent intrathoracic disguises.

4) Positive bronchoscopic biopsies were obtained in only 45 per cent of these patients, indicating the necessity for early exploration of suspicious lesions even without the preoperative confirmation of laboratory tests.

5) Resection of 35 solitary peripheral lung nodules proved 67 per cent to be some type of primary neoplasm.

RESUMEN

1) Las muertes por cáncer del pulmón representan un 10 por ciento de todas las muertes por cáncer, lo que coloca al cáncer de las vías respiratorias en segundo lugar sólo al cáncer del aparato intestinal.

2) El diagnóstico demorado redujo el índice de operabilidad en esta serie de 200 pacientes al 20 por ciento. Al 43.5 por ciento de estos pacientes se les halló ser inoperables en el examen clínico y a un otro 32.5 por ciento se les encontró ser inoperables durante la exploración.

3) Síntomas referidos al abdomen y a las extremidades fueron los más frecuentes disfraces extrapulmonares que demoraron el diagnóstico. La neumonía de virus, el absceso pulmonar, tuberculomas y tumores mediastínicos fueron los disfraces intratorácicos más frecuentes.

4) Se obtuvieron biopsias broncoscópicas positivas solamente en el 45 por ciento de estos pacientes, lo que indica la necesidad de la temprana exploración de lesiones sospechosas, aún sin la confirmación preoperatoria de pruebas de laboratorio.

5) La resección de 35 nódulos pulmonares periféricos solitarios resultaron ser algún tipo de neoplasma primario en el 67 por ciento de los casos.

RESUME

1) Les morts par cancer du poumon reprèsentent environ 10% de toutes les morts par cancer. Ainsi les cancers des voies respiratoires se placent en second, immédiatement après les cancers de l'intestin.

2) Un diagnostic trop tardif a réduit à 20% les possibilités opératoires de cette série de 200 malades. 43.5% de ces malades se montrèrent inopérables au simple examen clinique, et 32.5% se montrèrent inopérables lors de l'intervention.

3) Des symptômes ayant trait aux affections de l'abdomen ou des membres sont les causes extra-pulmonaires qui ont le plus souvent trompé et retardé le diagnostic. Les erreurs d'affections intrathoraciques consistèrent surtout en des diagnostics de pneumonie atypique, abcès du poumon, tuberculose, et tumeur du médiastin.

4) Ce n'est que dans 45% des cas que les biopsies bronchoscopiques se montrèrent positives, ce qui indique qu'il faut de toute nécessité en présence de lésions suspectes faire une thoracotomie exploratrice, même sans la confirmation pré-opératoire du laboratoire.

5) L'exérèse de 35 nodules pulmonaires isolés et situés près de la corticalité se sont montrés dans 67% des cas être de nature positive.

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Discussion

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The early diagnosis of bronchial carcinoma has been preached effectively during the past several years, so much so that in many cases the diagnosis was made too early, and lobectomies and pneumonectomies have been performed to find that no malignant condition was present. One clinic recently reported six cases in which lobectomy was performed for carcinoma and in each case the histological examination proved the condition to be chronic pneumonitis. In Dr. Poppe's series one third of the resected lung nodules were non-cancerous. In many of Dr. Poppe's cases the lung cancer developed silently and the patients presented themselves with complaints referable to the brain, the bones, or the intestinal tract. We have had similar experiences, and the presenting symptoms were attributable to metastatic tumors in the brain, spine, or liver. How can one hope to diagnose bronchial carcinoma in the operable stage in these cases?

In our efforts at early diagnosis of bronchial carcinoma we have made a few errors, which I hope you will find interesting.

There was the case of a 45 year old man who during the fall of 1941 had a chronic cough with pains in the left chest. The sputum smears were negative for acid fast bacilli. There was atelectasis of the left lower lobe, and the bronchoscopic examination showed a mass in this bronchus. The bronchogram showed lack of filling of the lower lobe. We diagnosed carcinoma of the lung and sent the man to our Tumor Center in Bronx, New York. While there, the bronchoscopic observations of obstructive lesion in the bronchus was confirmed, but the sputum was found to contain tubercle bacilli. The man was returned to us with a diagnosis of uncomplicated pulmonary tuberculosis. I followed the case periodically, confident that carcinoma would manifest itself.

On August 1, 1949, there was further contraction of the left lung. A lesion was present in the right upper lobe, which was rather typically tuberculous in appearance. There was no carcinoma, after eight years' observation.

On September 11, 1946, an admission diagnosis showed kidney stones. A 50 year old man with large cervical lymph nodes and a mass in right lumbar region had necrosis of ninth and 11th ribs on the right, plus a large air cyst in the right lung. There was a wheeze heard over the upper lobe bronchus on the right side. No lung tumor was visualized on roentgenogram or bronchoscopically. Biopsy of cervical node pointed to primary bronchogenic carcinoma.

On February 13, 1947, a large mass had developed at base of right lung and in upper mediastinum enveloping the trachea. This patient first sought medical aid when bone metastasis developed.

On October 22, 1947, a 60 year old male, ill two months, showed cystic emphysema, right upper lobe and left apex, and also a large mass in left upper lobe. Two Papanicolaou stains of sputum reported positive for tumor cells. Stricture in left upper lobe bronchus was seen bronchoscopically. However, sputum culture was surprisingly found positive for acid fast bacilli. A course of streptomycin was given with benefit. In view of the congenital cystic emphysema, which is prone to malignant degeneration, we felt that the original diagnosis of carcinoma was correct.

On September 9, 1949, the man's physical condition was satisfactory. The lesion in the left upper lobe had contracted and had lost its spherical appearance. We no longer entertained the suspicion of cancer.

A 48 year old male, on September 1, 1936, showed congenital cystic emphysema involving the entire right lung. Bronchoscopically there was obstruction in right main bronchus.

On April 6, 1948, this patient had had recurrent hemoptysis. Fusiform mass in right lung was replacing the air cyst which had become atelectatic. Clinical diagnosis was bronchogenic carcinoma in congenital cystic emphysema of the lung. Follow-up examination showed the man was still living 12 years after the diagnosis of carcinoma was made. The cyst had reexpanded. The atelectasis was ascribed to a blood clot in the neck of the air cyst.

Another case showed a round shadow which proved to be a cold abscess associated with tuberculosis of sternum.

Another interesting aspect was a large mass at base of the left lung in a cachectic individual of 56. Swallow of barium proved the mass to be an intrathoracic stomach (hernia of the diaphragm).

Amebic Lung Abscess*

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The availability of antibiotic and chemotherapeutic agents makes the prompt etiologic diagnosis of lung abscess highly desirable. That an amebic abscess of the liver may rupture through the diaphragm with resultant empyema, lung abscess, or bronchohepatic fistula is common knowledge. The occurrence of amebic lung abscess in persons without other signs or symptoms suggestive of amebiasis has been infrequently reported[3-7,12,17] yet the admission of four such cases to one military hospital in the United States in less than 18 months indicates the importance of considering this diagnosis.

Asymptomatic intestinal amebiasis is reported to be present in 5 to 20 per cent of the general population of the United States [1]. Veterans have shown an increased incidence of active, virulent amebiasis. There is also some evidence to indicate that Endamoeba histolytica acquired in the Pacific or China-Burma-India theaters is more prone to produce hepatic or pleuropulmonary disease than is our indigenous parasite.[9] Extra-intestinal amebiasis most frequently involves the liver, lung, and brain. Ochsner and Debakey found amebic abscess of the liver in 15 per cent of 388 cases of active amebic dysentery; 1.8 per cent of the 388 also had pleuropulmonary involvement. In 14 per cent of 153 cases of pleuropulmonary amebiasis, the lung abscess was considered to be hematogenous in origin and not associated with liver abscess[12].

It is generally believed that pulmonary involvement is always secondary to intestinal infestation, and two pathways of spread to the lung are suggested: (a) from the rectal hemorrhoidal veins by direct anastomoses to the inferior vena cava, and (b) more commonly, by the portal vein to the liver, with the formation of an abscess (which may be unrecognized), thrombophlebitis of some of the smaller radicles of the hepatic vein, and dissemination of amebae into the inferior vena cava [6,17]. In approximately 75 per cent of the cases, the abscess ruptures directly through the diaphragm, and it is not necessary to postulate an amebic septicemia. Entrance of amebae into the vertebral system of veins with its few valves, alternating direction of flow, and multiple anastomoses with the

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other venous systems would explain cerebral, pulmonary and other abscesses without passage of amebae through the liver[2].

The clinical features of amebic lung abscess resemble those of any pulmonary suppuration. It is characterized by fever, cough, pain in the chest, blood-tinged sputum, and the physical findings of pneumonitis or abscess: inspiratory lag on the involved side, some dulness on percussion, and rales over the involved portion of the lung. The lesion cannot be differentiated by roentgenogram from a pulmonary abscess due to other causes. Cavitation is common, and may lead one to think of tuberculosis. No significance can be attached to the failure to obtain a history of previous amebiasis, or of diarrhea. The finding of Endamoeba histolytica in the sputum is diagnostic; in the stools, suggestive. Failure to find the parasite does not rule out the disease. The complement fixation test, if positive, is strong circumstantial evidence. The blood count shows no characteristic changes, and the leucocytes are apt to be normal in number and character. Eosinophilia is not a feature of amebiasis. Lack of a causative organism in cultures of the sputum, failure to respond to penicillin, sulfadiazine and streptomycin, are minor points favoring the diagnosis. Response to emetine has been accepted as valid evidence that the disease was due to amebae [4,5,7-9,13]. Emetine effect is specific and restricted to amebae and Paragonimus westermani, although one author reports favorable clinical response to emetine in a series of furuncles of the lip and in cases of peritonitis[10]. Recent work has demostrated the efficacy of chloroquine, bacitracin, and aureomycin[11] in the treatment of various phases of amebiasis. We were fortunate enough to have inadvertently treated our Case 1 with aureomycin, with beneficial results.

Report of Cases:

Case 1: A 25 year old white male was admitted to the hospital March 28, 1949 with a two-day history of moderate fever, cough productive of greenish sputum, and pain in the right chest. He had been born in Manchuria, lived there until the age of six, then moved to Northern China. He had spent some time in India, North Africa, the Mediterranean countries, and the Philippines. He had never had any serious illness, and did not recall ever having diarrhea.

Physical Examination was within normal limits except for moderate pallor, temperature 99.6 degrees F., moderate injection of the pharynx, bulging of the right chest posteriorly, marked dullness, diminished vocal fremitus and a few rales over the lower third of the right chest, posteriorly and laterally.

The white blood count was 10,500 with a normal differential. Urinalysis and serology were negative. Erythrocyte sedimentation rate was 35 mm. per hour. Repeated sputum examination and culture revealed only common mouth organisms. Stool examination revealed cysts and trophozoites of Giardia lamblia.

Course in Hospital: Roentgenogram of the chest on admission showed a diffuse homogeneous density extending from the right hilum into the

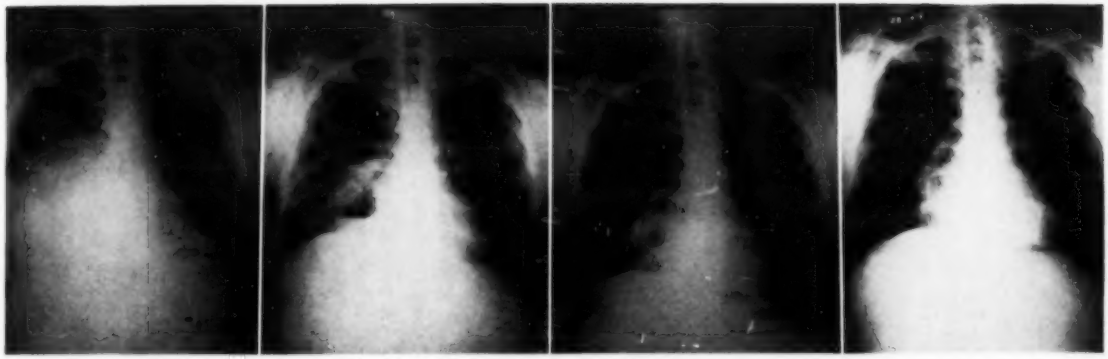

FIGURE 1 FIGURE 2 FIGURE 3 FIGURE 4

Amebic Abscess of the Lung Treated with Aureomycin.

Figure 1: Extensive pneumonitis of right middle and lower lobes. Prior to therapy.—*Figure 2:* After five days of aureomycin therapy.—*Figure 3:* After 20 days of aureomycin therapy.—*Figure 4:* After three days of emetine therapy. Abscess healed.

right base, suggesting a segmental type of pneumonia. A small amount of fluid was observed in the costophrenic angle posteriorly. Penicillin therapy was begun immediately, 100,000 units intramuscularly every three hours. He became progressively worse, and the temperature increased slightly. On the third hospital day, the amount of sputum increased to 400 cc. daily and became blood-tinged. Chest x-ray examination (Figure 1) revealed extensión of the infiltration to involve both the right middle and lower lobes. The amount of fluid was increased. Penicillin was discontinued at this time and aureomycin therapy instituted, four grams daily by mouth. Within 24 hours, he became afebrile, the sputum lost its blood-tinge, and his general appearance improved. By the fifth day of aureomycin therapy, he felt quite well except for the daily production of about 100 cc. of greenish, odorless sputum. X-ray film now showed considerable clearing of the area of infiltration and disappearance of the pleural effusion, but a cavity 4x8 cm. had appeared and contained both air and a fluid level (Figure 2). Blood was forwarded to the National Institute of Health at this time for a complement fixation test for amebiasis.

Aureomycin therapy was continued; x-ray inspection April 11 showed a 50 per cent decrease in the size of the cavity. Bronchoscopy, April 18, revealed pink, frothy sputum coming from the right lower lobe bronchus, but no evidence of foreign body. A report that the complement fixation test for amebiasis was positive was received April 19. The cavity at this time was small (Figure 3). Aureomycin therapy was discontinued, a total of 58 grams having been given. Emetine hydrochloride .065 grams was given daily by the intramuscular route, April 22 to May 1, and again June 29 to July 7. Sputum decreased to 30 cc. grayish mucoid material after one day of emetine therapy. The chest roentgenogram was considered to be normal April 25, 1949 except for minimal scarring at the site previously occupied by the abscess (Figure 4). No electrocardiographic abnormalities were detected during the period of emetine therapy nor the 10 days following completion of therapy. An x-ray film of the chest in October, 1949, was reported as negative.

Case 2: A 34 year old white male was admitted to the hospital October 18, 1949 complaining of general malaise, cough, and chilly sensation of one week's duration. He had produced a very small amount of rusty sputum on the two days preceding admission, and there was pain in the right infrascapular and right pectoral regions, worse on deep breathing or coughing. There were no symptoms referable to the gastro-intestinal tract or to the other body systems. He had received 2 grams of sulfadiazine on the day preceding admission. There was no history of previous serious illness; he had returned from a 28-month tour of duty in the Philippines and Japan in December, 1947. He could recall a two-day bout of diarrhea, but no other illness.

Physical Examination was not remarkable except for a slight nasal discharge, diminished breath sounds, a few fine moist rales below the right scapula, and questionable signs of cavitation over the third right intercostal space in the mid-clavicular line. Temperature, pulse, and respirations were normal.

The white blood count was 8,600, the differential normal. Erythrocyte sedimentation rate was 23 mm. per hour. No parasites were seen in two stool examinations. Sputum culture showed an alpha hemolytic streptococcus. X-ray film of the chest showed an area of increased density behind the right second rib.

Course in Hospital: Temperature rose to 101 degrees F. on the day of admission, and crystalline penicillin, 200,000 units, was administered intramuscularly every eight hours from October 18 to 25. The patient became afebrile October 19 but continued to cough, bringing up a small amount of rusty sputum. The chest roentgenogram October 20 (Figure 5) revealed a definite cavity in the right upper lobe, surrounded by a considerable area of increased density. Re-examination of the previous x-ray film showed this cavity to have been present initially. Because of our previous experience, the patient was urged to cough forcibly, and on the morning of October 21 a specimen of rusty sputum was obtained which contained many actively motile trophozoites of Endamoeba histolytica.

Therapy with emetine hydrochloride, .065 grams intramuscularly daily, was begun immediately and continued for 10 days. Diodoquin, 0.63 grams, was given three times daily for 20 days. After three days of emetine therapy, on October 24, the chest x-ray film showed marked reduction in the size of the cavity and in the extent of the inflamatory process. By November 2, there was further improvement, and the cavity, though small, was still visible (Figure 6). He was granted sick leave. Chest x-ray film was entirely clear by November 9, and he was returned to duty November 18 to receive a 10 day course of aureomycin as follow-up therapy. No electrocardiographic abnormalities were detected during or following his treatment with emetine. Complement fixation tests done October 21 and November 18 were negative.

Case 3: A 33 year old Negro male was admitted to the hospital October 31, 1949 complaining of fever and productive cough. His illness had

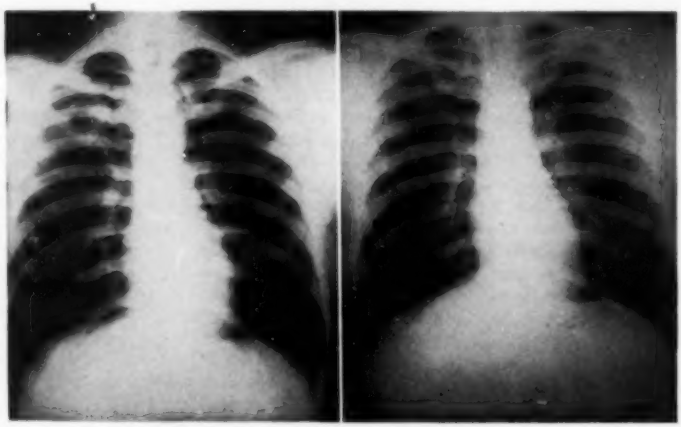

FIGURE 5 FIGURE 6

Amebic Abscess of the Lung Treated with Emetine.

Figure 5: Cavitation beneath the anterior portion of the right second rib with considerable surrounding pneumonitis. Trophozoites of Endamoeba histolytica were found in the sputum.—*Figure 6:* After completion of emetine therapy. A small cavity remains, but healed completely within one more week.

begun October 22, 1949 with a dry cough and fever. An x-ray film of the chest taken October 25, 1949 was reported normal, but the next day he began "to smell decay" when he coughed. After a period of strenuous exercise on October 28, he became exhausted and began to cough up material which looked "like curdled milk" but was pink in color. There were no symptoms of gastro-intestinal disease.

This patient had served in the Philippines, Italy, Japan, and Germany, but had not been out of the United States since October, 1947. He had had no previous illness except for a bloody diarrhea for 10 days in 1946 at Naples, Italy. The cause of this was not known to the patient and it did not appear that he had been treated for amebiasis.

Physical Examination revealed a moderately ill, thin, well-developed Negro with no abnormal physical findings. Temperature was 100 degrees F, pulse 102, respirations 20. The white blood count was 10,700 with a normal differential. The erythrocyte sedimentation rate was 34 mm. per hour. Sputum examination repeatedly failed to reveal acid-fast bacteria or amebae; culture showed only a gram-positive micrococcus and diphtheroids. X-ray film of the chest November 1, 1949 revealed a cavity 2.5 by 1.5 cm. in the right lung field just lateral to the hilum. The cavity was surrounded by a definite area of infiltration. Liver function tests were within normal limits.

Course in Hospital: Procaine penicillin, 300,000 units daily, was administered November 1 to 5. The temperature, which had risen to 102 degrees F., the night of admission, returned to normal by the fourth hospital day. He continued to bring up about 100 cc. of red-brown, mildly malodorous sputum each day. Stool examinations revealed cysts and trophozoites of Endamoeba coli, ova of trichurius trichuria, and cysts suggestive of, but not diagnostic of Endomoeba histolytica.

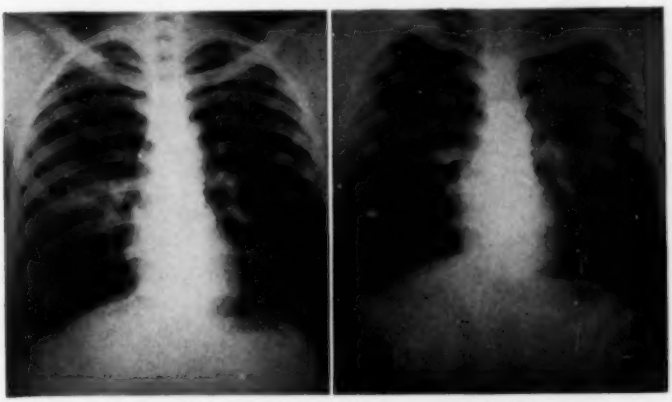

FIGURE 7 FIGURE 8

Figure 7: After five days of penicillin therapy with little change from the admission roentgenogram. Penicillin discontinued, emetine therapy begun.—*Figure 8:* After nine days of emetine therapy. There was a definite shrinkage of the cavity and thinning of the wall of reaction after two days of emetine therapy. Complete clearing occurred subsequently.

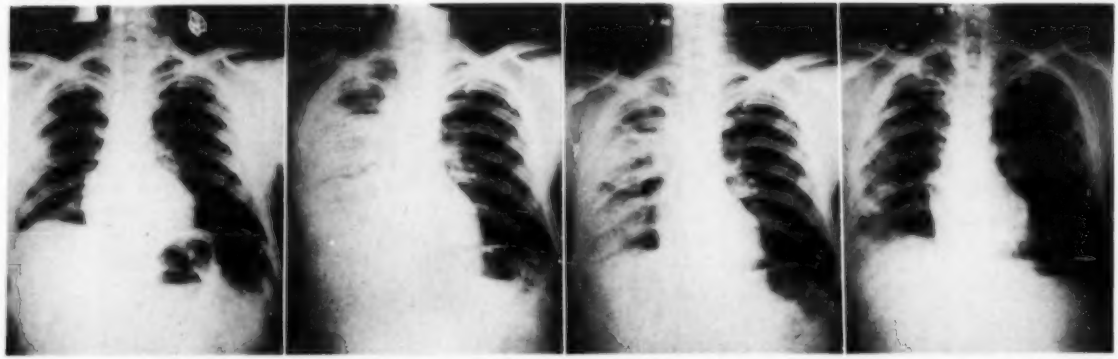

FIGURE 9 FIGURE 10 FIGURE 11 FIGURE 12

Amebic Pleuritis and Lung Abscess Treated with Emetine.

Figure 9: Initial area of pneumonitis in the right mid-lung field. Five days later, fluid obscured lower two-thirds of the right lung field and multiple areas of loculated fluid were seen over the upper third of the field.—*Figure 10:* After four days of emetine therapy, much of the fluid has been absorbed. — *Figure 11:* Further improvement at the completion of nine days of emetine therapy.—*Figure 12:* Ten days later, there has been absorption of the encapsulated fluid and resolution of much of the pneumonitis. Pneumothorax was inadvertently induced during attempted aspiration of fluid.

Because our Case 2 was still a hospital patient, the possibility that this was an amebic lung abscess was immediately considered. History of previous tropical service, the episode of diarrhea in 1946, the failure to find bacteriologic or other reason for the abscess, and the suggestive stool findings were considered sufficient reason for a therapeutic trial of emetine. Accordingly, the penicillin was discontinued and emetine, .065 grams, was given daily November 5 to 14 inclusive. There was immediate symptomatic improvement, and within 24 hours, the sputum had lost its pink tinge and been reduced in amount from 100 cc. to 50 cc. There was a small amount of sputum the next day, none thereafter. An x-ray film of the chest was made on November 5 prior to emetine therapy (Figure 7). This showed little change from the previous one, except for the presence of a definite fluid level. After two days of emetine therapy, another film showed marked improvement with definite shrinkage of the cavity, thinning of the wall of reaction, and disappearance of the fluid level. Serial roentgenograms showed rapid and continued improvement. After nine days of emetine therapy, the wall of reaction had disappeared and difficulty was experienced in outlining the cavity (Figure 8). He was then given a course of diodoquin, 0.63 grams, three times daily for 20 days, and returned to duty. Serial electrocardiograms revealed no abnormality. Complement fixation tests for amebiasis taken before and after emetine therapy were negative.

Case 4: A 23 year old white male veteran was admitted to the hospital September 18, 1948, complaining of weakness, chills, fever, anorexia, and pain in the right chest. He had spent considerable time in Cuba and in the South Pacific, but had never had malaria or any form of dysentery. He was completely well until May 30, 1948, when he received several superficial knife wounds over the right scapula and in the right axilla posteriorly. These were sutured and healed well, but one week later he began complaining of right-sided chest pain. X-ray examination of the chest at this time was negative. For the next five weeks, he became gradually sicker with chills, fever, anorexia, occasional vomiting, and the loss of 29 pounds in weight.

On July 21, 1948 he entered a civilian hospital, acutely ill with pain in the right chest and tenderness in the epigastrium and right lumbosacral region. Chest x-ray film revealed a small area of increased density in the mid-portion of the right lung. He was treated with penicillin and streptomycin, but his temperature continued to fluctuate between 100 and 103 degrees F. Five days later, a second chest x-ray film showed an increase in the size of the infiltrate in the right lung. Concomitantly, he developed pain and tenderness over the entire right leg. On August 2, 1948 he was transferred to our military hospital. A diagnosis of thrombophlebitis of the deep veins of the right leg was made and dicoumarol therapy instituted. X-ray examination of the chest revealed the previously described area of increased density. This was thought to represent either a lung abscess or an area of infarction. Large doses of penicillin

were administered with little improvement, and he left the hospital August 24, against medical advice.

On September 13, 1948 he began to cough up moderate amounts of thick mucopurulent blood-streaked sputum. There was no dyspnea or cyanosis. He continued febrile and was re-admitted to the hospital September 18, 1948.

Physical Examination showed him to be thin, pale, and acutely ill. There was dullness in the right axilla and right base posteriorly. Crepitant rales were heard over the right lower lobe of the lung. The abdomen was soft, non-tender, and the liver was not felt. The ankles and toes were thought to be slightly edematous.

White blood count was 10,860 with a normal differential. The erythrocyte sedimentation rate was 33 mm. per hour. Sputum culture showed hemolytic and non-hemolytic staphlococcus aureus and alpha hemolytic streptococci.

X-ray inspection of the chest September 20, 1948 (Figure 9) revealed a triangular area of density in the right lower lobe, similar in appearance to fluid, but consistent with a diagnosis of pneumonia, infarct, or lung abscess.

Course in Hospital: Temperature was 99.4 degrees F. each day for the next week. Pain in the right anterior chest and a non-productive cough were present. He vomited frequently. Therapy consisted of 100,000 units of penicillin every three hours, dicoumarol, whole blood transfusions, and intravenous fluids. By September 25, it was evident that he had developed a pleural effusion, and x-ray inspection showed the entire lower two-thirds of the right lung field obscured by an homogeneous density and partial obscuration of the right upper lobe. There were areas of loculation of fluid. The liver became palpable at this time, extending three finger-breadths below the costal margin. He began to cough up large quantities of thick mucopurulent sputum which was blood-tinged. Because of his history of tropical service and the sudden appearance of "anchovy-sauce" sputum, it was felt that he might have an amebic lung abscess which had ruptured into a bronchus, and associated amebic pleuritis. No amebae were found in the sputum.

Emetine hydrochloride, .065 gram, was given daily from September 26 to October 2. Temperature fell promptly and became completely normal within four days; the quantity of sputum diminished from 300 cc. per day to 15 cc. of thin, clear mucoid material daily. There was some improvement in the chest x-ray film by September 30 (Figure 10), with absorption of much of the fluid from the right pleural cavity, although multiple fluid levels were still present, and the previously noted area of pneumonitis persisted. When emetine therapy was discontinued October 2, he was entirely asymptomatic and the appearance of the chest x-ray film was considerably improved (Figure 11). Aspiration of the chest was attempted but no fluid could be obtained; however, partial pneumothorax was inadvertently induced. Further improvement occurred rapidly, and the chest roentgen-ray film taken October 12 demostrated right pneumothorax, marked resolution of the pleural thickening,

and absorption of the encapsulated pleural fluid. Some fluid remained along the lateral chest wall (Figure 12).

On October 11, 1949 cysts and trophozoites of Endamoeba histolytica were found in the stool. Another course of emetine was given for eight days, followed by diodoquin for 20 days. Prior to discharge from the hospital, his chest showed complete clearing of the lung parenchyma, but a few areas of pleural thickening remained over the lateral aspect of the right lung field.

Discussion

In the four cases presented, considerable diagnostic importance has been attached to the response to emetine. The fallacies and disadvantages inherent in the use of therapeutic agents as a diagnostic measure are appreciated, yet the difficulty in obtaining direct evidence of etiology is such that indirect evidence must sometimes suffice. The only unequivocal proof that a pulmonary abscess is amebic in origin would be the recovery of Endamoeba histolytica trophozoites by aspiration of the abscess or by finding them in the sputum. The growth requirements of the parasite are such that it must live in viable tissue; it is not found in the detritus which fills the abscess, but in the wall of reaction surrounding it. It is possible that the forceful coughing required of our Case 2 may have dislodged minute particles of tissue from the abscess wall and so account for the presence of the trophozoites in the sputum. Less energetic measures were used in the other three cases, and this may account in part for our failure to identify the parasite in the sputum of those cases.

The complement fixation test was not attempted in Case 4; it was positive only in Case 1. Terry and Bozicevich[16] do not believe that false positives occur with the test, and the instances of negative results in their series of amebic abscess of the liver are explained as technical errors due to the use of an antigen of insufficient potency. The test was repeatedly negative in our Cases 2 and 3. Neither of these patients had been ill more than two weeks when definitive therapy was begun with emetine. There was no evidence of amebic hepatitis in either. It would seem fair to assume that either there was technical error in performing the repeated tests, or that the infestation was not of sufficient duration or severity to produce the immunological changes necessary for a positive test.

The presence of trophozoites or cysts of Endamoeba histolytica in the stool is not conclusive evidence that a lung abscess is due to this organism, since such a large percentage of the population is infested. Failure to find amebae is common, for few general clinical laboratories are willing to make the considerable expediture of

time and effort necessary for success. The amebae commonly live in the cecum; unless there is active dysentery, the trophozoites may well die before the stool is passed. The cysts which are included in the stool are not evenly distributed, so that the chance of their being overlooked is great.

Both emetine and aureomycin are effective drugs in the treatment of pulmonary amebiasis. The toxicity of each is slight, provided the dosage is not excessive or therapy prolonged unduly. So much is to be gained at so little risk that it is our opinion that pulmonary abscesses such as we have described should have a "therapeutic trial" of either emetine or aureomycin before more drastic therapy, such as surgery, is undertaken. Emetine is the drug of choice because it is effective only against amebic infections and does not have the anti-bacterial effects of aureomycin which would be confusing from a diagnostic standpoint. A safe and adequate dose is .065 grams of emetine hydrochloride intramuscularly daily for 10 days. This course may be repeated after a 10 day rest period, provided there have been no significant changes in the pulse rate, blood pressure, or electrocardiogram. Diodoquin, 0.63 grams three times a day for 20 days should be administered, either concurrently or following the emetine therapy, for its effect on the intestinal infestation always present in these cases.

The cases here presented demonstrate that amebiasis may be asymptomatic over a long period of time, and that when it does become active, it need not necessarily be accompanied by gastro-intestinal symptoms. Although most cases of amebic lung abscess have been exposed to tropical strains of Endamoeba histolytica, it is quite possible that such lesions result from infestation with other varieties of the parasite. The possibility of infestation by the tropical parasite within the United States is pointed out by Koszalka, et al[9]. Three of their cases of thoraco-hepatic amebiasis presumably acquired the infestation swimming in a pool used by a large number of veterans recently returned from the Pacific Theater.

SUMMARY

1) Four cases of lung abscess, presumably due to Endamoeba histolytica, without other signs or symptoms suggestive of amebiasis were admitted to one military hospital within 18 months. All had previously lived in the China-Burma-India or Philippine area, were unaware of amebic infestation, and had been in the United States for two or more years immediately preceding the present illness.

2) One case was treated with aureomycin with good results, all received emetine with dramatic effect upon the fever and quantity

of sputum; the pulmonary cavities closed promptly with minimal scarring.

3) It is recommended that cases of pulmonary abscess in which the usual causative agents have been excluded, and which do not respond to penicillin, streptomycin or sulfadiazine be given a therapeutic trial of emetine before resort is had to surgery. Response to emetine is felt to be indicative of the amebic etiology.

NOTE: Since the submission of this manuscript, the experience of the authors has led them to believe that aureomycin alone is not a satisfactory treatment for amebiasis, because of the high incidence of relapse. It is felt that emetine is necessary for satisfactory cure.

RESUMEN

1) En el término de 18 meses se admitieron en un hospital militar cuatro casos de absceso pulmonar probablemente debidos a la amiba histolítica sin otros síntomas sugestivos de amibiasis.

Todos habían vivido antes en China, Birmania y la India o en el área de las Filipinas y no se habían dado cuenta de la infestación amibiana y además habían permanecido ya en Estdos Unidos dos o más ños antes de que se presentara la enfermedad actual.

2) Un caso fué tratado con aureomicina con buenos resultados, todós recibieron emetina con sorprendentes resultados sobre la fiebre y sobre la cantidad de esputos. Las cavidades pulmonares cerraron prontamente con el mínimo de cicatriz.

3) Se recomienda que los casos de absceso pulmonar en los que los agentes habituales hayan sido excluidos y que no responden a la penicilina, estreptomicina o sulfatiazol, sean sometidos a tratamiento de prueba antes de hacer nada quirúrgico. La respuesta a la emetina se considera que indica la etiología amibiana.

RESUME

1) Quatre malades atteints d'abcès du poumon ont été admis dans un hôpital militaire en 18 mois. Il est problable que ces abcès étaient dus à *Entamoeba histolyca* sans que l'on puisse noter aucune autre minifestation d'amibiase. Tous avaient séjourné en Chine, aux Indes ou aux Philippines et étaient de retour aux Etats-Unis depuis deux ans et plus quand survint l'affection actuelle.

2) Un cas fut traité par l'aureomycine avec de bons résultats. Tous furent soumis à l'action de l'emetine qui fut tout à fait spectaculaire sur la fièvre et l'expectoration. Les cavités pulmonaires se fermèrent rapidement ne laissant que des traces cicatricielles minimes.

3) Les auteurs conseillent de faire un traitement d'épreuve à l'émétine dans les abcès du poumon dont l'origine reste indéterminée, et qui résistent aux antibiotiques et aux sulfamides. Ce

n'est qu'après cet essai qu'ils pourront être confiés au chirurgien. Une réponse favorable à la thérapeutique par l'émétine est un argument en faveur de l'étiologie amibienne.

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Pulmonary Decortication*

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Pulmonary decortication is, relatively speaking, an old operative procedure, which gained a fresh impetus during the second world war. George R. Fowler[1,2] performed this operation in 1893 with gratifying results in all cases of old empyemas where pulmonary tuberculosis had been excluded, and the patient's condition permitted major surgery. Delorme[3] in 1894 performed an operation similar to that of Fowler.

Briefly the operation consists of widely opening the thoracic cage either by incision through the fifth intercostal space, or by excision of the sixth rib, and of extirpating the visceral, diaphragmatic and parietal pleurae; where indicated, visceral and diaphragmatic pleurectomy alone is adequate. Post operatively air-tight, water-sealed, or in some cases suction drainage is used. The drainage tube is removed as soon as the lung has fully expanded.

Due to the extraordinary developments in anaesthesiology, the discovery and use of new drugs including antibiotics, better understanding of pre-operative preparation and post-operative care, this procedure is now applicable to many pleuro-pulmonary pathological conditions. It has, for example, partially solved the problem of the unexpanded post-pneumothorax lung with or without effusion. We are now performing pleurectomy in such cases provided, after careful study of all previous chest x-ray films including laminographs, we are convinced that the cavity is closed, and the original disease arrested. In one case the unexpanded post-pneumothorax lung, which had existed nine years, became fully expanded the first day post-operatively (Figures 1, 2 and 3).

These same criteria, and operative procedures apply to tuberculous empyema for which we formerly did thoracoplasties. The results were not always good, as a slit empyema cavity often remained. Then, we performed various modifications of the Schede operation. Often, after subjecting the patient to several surgical procedures a draining sinus remained. As a result of this experience in the old cases, on whom we had performed thoracoplasty for closure of tuberculous empyema, and had failed, we are now

*Address given at the Annual Meeting of the Society of Surgeons of New Jersey, held at the Jersey City Medical Center, Jersey City, November 16, 1949.

†Chief of Thoracic Surgery, Berthold S. Pollack Hospital for Diseases of the Chest, Jersey City Medical Center.

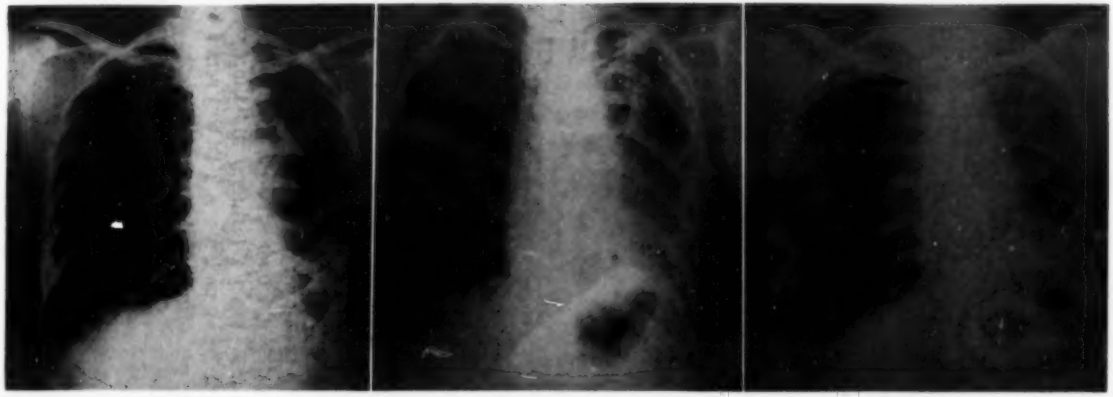

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Unexpanded post pneumothorax lung of nine years duration.—*Figure 2:* One day post-operatively.—*Figure 3:* One year post-operatively.

following up with decortication, rather than the Schede operation, with good results. Where we had performed thoracoplasties to close cavities in upper lobes, in which there was an associated tuberculous empyema, or when empyema developed after thoracoplasty which had failed, we are now performing lobectomy plus decortication of the remaining lower lobes with good results.

The experience acquired by physicians with chest injuries during World War II has placed the treatment of hemothorax on a sound basis. Now we first do thoracentesis. Neglected organising hemothorax may eventuate in a fibrothorax which may become infected. Procrastination in the treatment will permit such advanced organisation along the visceral pleural surface that the lung becomes encased in fibrous tissue so dense that its expansion cannot occur. The best treatment therefore, as soon as the patient's condition warrants, is to open the pleural cavity, evacuate the blood clots and perform pulmonary decortication.

This operative procedure also has revolutionized the treatment of non tuberculous empyema. The majority of cases recover with modern drug therapy coupled with repeated thoracenteses. If the temperature remains elevated in spite of this treatment, and fluid continues to accumulate, preventing the lung from re-expanding, a rib should be resected and tube drainage instituted. If the temperature and pulse rate improve however, but the fluid continues to collect, the thoracic cage should be widely opened, and pleurectomy performed followed by air-tight, water-sealed drainage. If, after rib resection and tube drainage, the temperature and pulse rate return to normal, but the lung still does not re-expand, rather than wait for months as we did in the past, we decorticate within a few weeks. If broncho-pleural fistula coexists, rib resection and tube drainage should be done immediately (Figures 4, 5 and 6).

With these avenues of approach which eliminate months of draining and waiting and hoping for closure, we can conclude that the problem of chronic empyema has been solved. In closing, I want to stress the importance in the advances in knowledge of the adjuncts to the actual surgery: the improved techniques in anesthesia, the existence of effective drugs to combat infection, and the better management of the surgical patient. Because of these factors alone, the old operation of pulmonary decortication has returned to replace the deforming surgical procedures of the past.

SUMMARY

1) Pulmonary decortication was successfully performed in the 1890's.

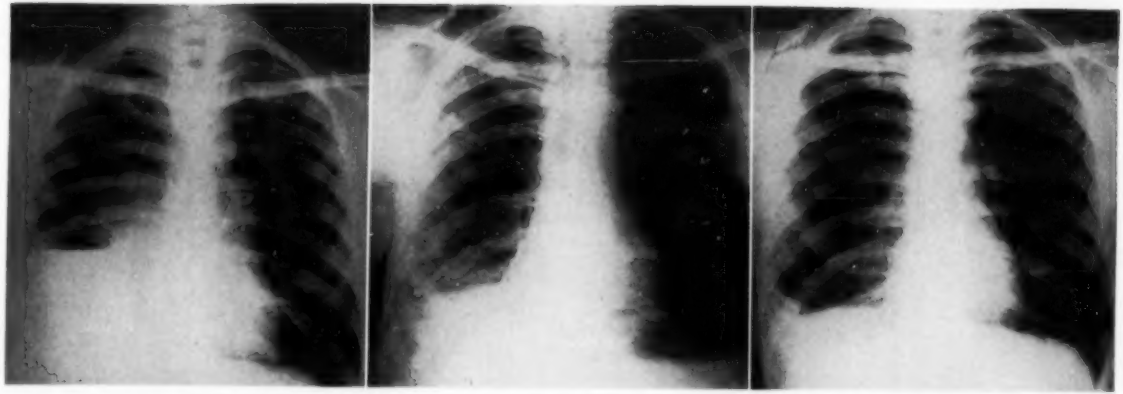

FIGURE 4 FIGURE 5 FIGURE 5

Figure 4: Empyema, repeated thoracenteses not benefitted by drugs including antibiotics.—*Figure 5:* Decortication, one day post-operatively.—*Figure 6:* Present status, 26 days post-operatively.

2) In the last few years it has practically solved the problem of the unexpanded post-pneumothorax lung.

3) In tuberculous empyema decortication is now replacing the Schede operation. Cases of chronic non tuberculous empyema are also successfully treated by this operation.

4) Persons with hemothorax resulting from chest injuries can often be prevented from sustaining marked loss of pulmonary function if decortication is done sufficiently early.

RESUMEN

1) El descortezamiento del pulmón fue llevado a cabo con buen éxito un poco después de 1890.

2) En los últimos años casi que ha resuelto el problema del pulmón que no se reexpande después del neumotórax.

3) En el empiema tuberculoso el descortezamiento está reemplazando la operación de Schede. Casos de empiema crónico no tuberculoso también pueden ser tratados con buen éxito mediante esta operación.

4) En personas con hemotórax secundario a heridas torácicas, a menudo se puede evitar la pérdida decidida de función pulmonar si se emplea el descortezamiento lo suficientemente temprano.

RESUME

1) Il y a déjà longtemps que l'on pratique avec succès la décortication pleurale.

2) Dans ces dernières années, grâce à cette intervention, on a trouvé la solution pratique du problème que pose l'absence de réexpansion pulmonaire après pneumothorax.

3) Dans l'empyème tuberculeux, la décortication remplace maintenant l'opération de Schede. On peut traiter également avec succès par cette intervention les ampyème chroniques non tuberculeux.

4) Pour les individus qui sont atteints d'hémothorax, à la suite de traumatismes thoraciques, on peut souvent éviter une perte importante de la fonction pulmonaire si la décortication pleurale est pratiquée à temps.

FOURTH ANNUAL POSTGRADUATE COURSE IN DISEASES OF THE CHEST

Warwick Hotel, Philadelphia, Pennsylvania, March 26-30, 1951

Some of the physicians and lecturers who participated in the Fourth Annual Postgraduate Course in Diseases of the Chest presented in Philadelphia, March 26-30, 1951.

Philadelphia Postgraduate Course

The Fourth Annual Postgraduate Course in Diseases of the Chest sponsored by the Pennsylvania Chapter, American College of Chest Physicians and the Laennec Society of Philadelphia was presented at the Warwick Hotel, Philadelphia, during the week of March 26-30. A photograph of some of the physicians and lecturers in the course is shown on the opposite page. Fifty-four physicians were registered for the course. The course was organized and conducted by a committee composed of Dr. Chevalier L. Jackson, Chairman, Dr. Leon H. Collins Jr., Vice-Chairman, Dr. Katharine R. Boucot, Dr. Louis Cohen, Dr. Robert V. Cohen, Dr. David A. Cooper, Dr. J. Antrim Crellin, Dr. Burgess L. Gordon, Dr. William A. Lell, Dr. Esmond R. Long and Dr. Martin J. Sokoloff. Dr. J. Winthrop Peabody, Washington, D. C., chairman of the Council on Postgraduate Medical Education of the College, and Dr. Edward Lebovitz, Pittsburgh, President of the Pennsylvania Chapter of the College, served as ex-officio members of the committee.

Correction

Legends appearing in the article, "Angiocardiographic Findings in Pulmonary Tuberculosis" by Israel Steinberg, M.D., F.C.C.P., Herbert I. McCoy, M.D. and Charles T. Dotter, M.D., published in the May 1951 issue of *Diseases of the Chest*, should be corrected as follows:

Legend mistakenly reproduced as Figure	*Actually belongs with Figure*
1	7
2	1
6	8
7	2
8	6

College Chapter News

CALIFORNIA CHAPTER

The California Chapter of the College held its annual meeting in Los Angeles on May 12 at which time the following officers were elected for the coming year:

Jane Skillen, Olive View, President
William Cassidy, Livermore, Vice-President
Alfred Goldman, Los Angeles, Secretary-Treasurer.

Alfred Goldman, Secretary.

FLORIDA CHAPTER

The Florida Chapter of the College held its annual meeting in Hollywood on April 22 in conjunction with the meeting of the Florida State Medical Association. The following officers were elected for the coming year:

Howard K. Edwards, Miami, President
Alexander Libow, Miami Beach, Vice-President
Nathaniel M. Levin, Miami, Secretary-Treasurer.

Dr. DeWitt C. Daughtry of Miami was appointed chairman of the program committee for the chapter.

Nathaniel M. Levin, Secretary.

MISSOURI CHAPTER

The Missouri Chapter of the College met in Kansas City on April 22, in conjunction with the meeting of the Missouri State Medical Association. The following officers were elected for the chapter:

Elmer E. Glenn, Springfield, President
Lawrence E. Wood, Kansas City, Vice-President
Alexander J. Steiner, St. Louis, Secretary-Treasurer.

A. J. Steiner, Secretary.

NEW ENGLAND STATES CHAPTER

The New England States Chapter of the College held its annual meeting at the Deaconess Hospital, Boston, Massachusetts, on May 9, 1951. Dr. Dwight E. Harken, Boston, spoke on "Recent Developments in Intracardiac Surgery." At the business session the following officers were elected for the coming year:

Moses J. Stone, Boston, Massachusetts, President
Maurice Kenler, New Bedford, Massachusetts, Vice-President
John B. Andosca, Boston, Massachusetts, Secretary-Treasurer.

John B. Andosca, Secretary.

NEW JERSEY CHAPTER

The annual meeting of the New Jersey Chapter of the College was held in Atlantic City on May 15. The scientific session of the meeting was a joint program of the Section on Diseases of the Chest and the Section on Heart Diseases of the New Jersey State Medical Society. Speakers included Dr. Howard B. Sprague, President, American Heart Association; Dr. Henry K. Taylor, New York University; Dr. Samuel Bellet, University of Pennsylvania; Dr. Jerome G. Kaufman, President, New Jersey Heart Association; and Dr. Charles P. Bailey, Philadelphia.

The annual chapter meeting included a luncheon at the Chalfonte Hotel and a feature during this luncheon was an x-ray "Information Please" program conducted by Dr. Henry K. Taylor.

The following officers of the chapter were elected for the coming year:

John Runnells, Scotch Plains, President
Juan R. Herradora, Jersey City, First Vice-President
J. Earle Stuart, Plainfield, Second Vice-President
Irving J. Selikoff, Paterson, Secretary-Treasurer.

Irving J. Selikoff, Secretary.

NEW YORK STATE CHAPTER

The annual meeting of the New York State Chapter of the College was held in the Empire State Room of the Hotel Statler, Buffalo, on May 3. Among the guests present at the dinner meeting were Dr. J. Stanley Kenney, President of the Medical Society of the State of New York; Dr. Walter P. Anderton, Secretary and General Manager of the Medical Society of the State of New York; Dr. Charles P. Bailey, Hahnemann Medical College of Philadelphia, the guest speaker; and Dr. Ethan Flagg Butler of Buffalo, New York. The local committee chairman, Dr. Donald R. McKay, a member of the Board of Regents of the College, arranged the excellent cocktail party and dinner.

The Nominating Committee, under the chairmanship of Dr. J. Herbert Donnelly, Buffalo, presented the slate of officers for the year 1951-52, which was unanimously approved. The new officers for the year are:

Clyde George, Buffalo, President
Charles E. Hamilton, Brooklyn, First Vice-President
Leonard C. Evander, Lockport, Second Vice-President
Harry Golembe, Liberty, Secretary-Treasurer.

At the meeting of the Section on Diseases of the Chest in the New York State Medical Society, Dr. David Ulmar, New York, was elected Chairman of the Section, Dr. Arthur Q. Penta, Schenectady, Secretary, and Dr. Foster Murray, Brooklyn, Delegate.

Harry Golembe, Secretary.

PACIFIC NORTHWEST CHAPTER

The Pacific Northwest Chapter of the College will hold its annual meeting in Portland, Oregon on November 1 and 2, 1951. The meeting will follow a three day postgraduate course in diseases of the chest to be held at the University of Oregon Medical School, October 29-November 31. Announcements will be sent out in the near future and the program for the meeting will be published in the College journal as soon as it is available.

Byron Francis, Secretary.

PENNSYLVANIA CHAPTER

The Pennsylvania Chapter of the College is planning a meeting to be held jointly with the Laennec Society of Philadelphia in the early part of November, 1951. The program for the meeting will be published in a future issue of the journal.

John V. Foster, Secretary.

VIRGINIA CHAPTER

The annual meeting of the Virginia Chapter of the College was held in Richmond on April 25. The following officers of the chapter were elected for the year 1951-1952:

Charles P. Cake, Arlington, President
Bryan Grinnan, Norfolk, Vice-President
M. Foscue Brock, Norfolk, Secretary-Treasurer.

M. Foscue Brock, Secretary.

College News Notes

Dr. Ricardo Sanchez Acosta, Havana, Cuba, Secretary-Treasurer of the Cuban Chapter of the College, has been appointed medical director of the Sanatorio La Esperanza in Havana.

At the annual meeting of the Illinois Tuberculosis Association Dr. Fred M. F. Meixner, Peoria, Illinois, former Regent of the College and past-president of the Illinois Chapter, was presented with the Award for Distinguished Service of the Association for his outstanding work in the field of tuberculosis control in Illinois. He was also elected a member of the Board of Directors and the Executive Committee for life.

Dr. Maurice S. Segal, who has recently been promoted to Clinical Professor of Medicine, Tufts College Medical School, Boston, Massachusetts, has lectured during the past few months at the meetings of the Florida, New York State, Illinois and Wisconsin Chapters of the College. Dr. Segal spoke on the subject of ACTH and Cortisone in the Treatment of Pulmonary Diseases.

Dr. Benjamin L. Brock has been appointed medical director of the Central Florida State Sanatorium in Orlando. He assumed his duties at the sanatorium on July 1. Dr. Brock was formerly acting chief of the tuberculosis service, Veterans Administration Hospital, Downey, Illinois.

Dr. Frank R. Ferlaino, New York City, Assistant Clinical Professor of Industrial Medicine, Institute of Industrial Medicine, New York University Postgraduate Medical School, has been made a member of the Board of Trustees of the Society of Medical Jurisprudence. Dr. Ferlaino also serves as medical director in New York for General Motors Corp.

LAENNEC SOCIETY OF PHILADELPHIA

The Laennec Society of Philadelphia will award a prize of $200.00 for the best paper submitted in any field related to diseases of the chest. This prize is open to undergraduates, interns, residents, or Fellows throughout the United States. The work should be original and not a review of the literature or of previous contributions. The Society does not reserve the right of publication but requests the prize winning paper be presented at one of its regular scientific meetings.

Five copies of the manuscript should be submitted in the customary form for publication, i.e., double space and with wide margins. They should be in the hands of the Secretary of the Society, Dr. Katharine R. Boucot, 311 South Juniper Street, Philadelphia 7, Pennsylvania, by October 1, 1951.

Obituaries

GERMAINE A. GUNTZER
1899 - 1950

Dr. Germaine A. Guntzer was born in New York City, November 23, 1899. She was a graduate of Cornell University Medical College, New York City, in the class of 1931 and obtained her Master's degree in Public Health from Yale University Medical School in 1941. After completing a one-year rotating internship at the United Hospital, Port Chester, New York, in 1932, Dr. Guntzer served the next nine years in institutional work in tuberculosis at Grasslands Hospital, Valhalla, New York; Oneida County Sanatorium, Utica, New York; and the William Wirt Winchester Hospital, New Haven, Connecticut. On account of illness she was forced to give up her work in the latter part of 1942 and was hospitalized until 1945. After regaining her health, she joined the staff of the New York office of the National Tuberculosis Association as Medical Consultant for a good part of the year 1947. In December 1947, she joined the staff of Leahi Hospital, Honolulu, T. H., as a senior resident physician but was forced to give up active work because of illness in November, 1949. Her death came from cerebral hemorrhage on September 2, 1950 at Leahi Hospital after months of severe illness. Dr. Guntzer had a fine knowledge of her specialty and was skilled in the art of tuberculosis treatment. As is so frequently the case with phthisiologists, her knowledge was acquired in large measure from her personal experiences with the disease.

William F. Leslie, Governor for Hawaii.

ELLIOTT PLUMMER SMART
1895 - 1950

Dr. Elliott Smart, Fellow of the American College of Chest Physicians, died on the morning of October 13, 1950 of cerebral hemorrhage. This terminated an illness which began with a coronary occlusion May 26, 1950.

Dr. Smart was born at Blue Earth, Minnesota, on September 9, 1895. His early education was in the schools of his home town. While in childhood his father, Dr. Granville I. Smart was stricken with tuberculosis and the family moved to Ontario, California, with the hope that it would help him recuperate his health. This early association with tuberculosis undoubtedly played a part in developing an interest in chest diseases which later led to Dr. Elliott Smart specializing in this field.

Dr. Elliott Smart graduated from Chaffey Union High School in Ontario and then took his premedical and medical training at the University of Southern California from which he was graduated in 1912.

His first location after graduation was in Sand Canyon where he had charge of the Emergency Hospital for the Los Angeles Aqueduct Project. Following this he entered private practice at Ontario for one and one-half years and then left to take charge of a mining company hospital at Tumco, California. He returned to private practice in Lankershim, California in 1915 but shortly thereafter entered the National Guard and was called to duty in World War I. He served overseas with the 40th Division commanding the 157th Field Hospital. He attained the rank of major and held a colonel's rating in the reserve.

Following World War I he was in private practice for a short time and

then entered the United States Public Health Service and from there went to the Veterans Bureau and to Castle Point, New York, where he underwent special training in tuberculosis and chest diseases.

In 1925 he went to Olive View Sanatorium where he remained until 1936 in the capacity of Chief Resident Physician.

From 1936 until the time of death he served as Superintendent and Medical Director of Bret Harte Sanatorium at Murphys, California.

During his years of service he earned the respect of his confreres and the undying gratitude and appreciation of the patients who came under his care.

He was a member of the Masonic Lodge in Ontario, California, Veteran's of Foreign Wars, American Legion, and a member of the Boy Scouts Committee, Lions Club and he belonged to the following professional organizations, San Joaquin Tuberculosis and Health Association and was President of the Calaveras County Tuberculosis and Health Association, American Medical Association, American College of Physicians and American College of Chest Physicians, Trudeau Society and Western Hospital Association.

On January 15, 1913 he married Miss Ann MacArthur and there are four children, Annette Smart Hyde of Los Angeles, Elianna Smart Jones of Fort Monmouth, New Jersey, Elliott A. Smart, Student in school of Dentistry, Berkeley and JoAnne Smart Baldwin of Oakland, California.

Buford H. Wardrip, Governor for California.

FRANK LANDE
1889 - 1950

Dr. Frank Lande died August 28, 1950, aged 61. He graduated from the University of Louisville School of Medicine in 1921 and interned in Louisville City Hospital, Louisville, Kentucky. He did postgraduate work at Columbia University College of Physicians and Surgeons and also at the Harvard Postgraduate Medical School. He was a Fellow of the American College of Chest Physicians, a member of the Ohio State Medical Association, a Fellow of the American Medical Association, and a member of the American Society of Clinical Pathologists. For several years he was Director of the Rocky Glen Sanatorium and resigned in May, 1950, to resume the private practice of medicine. He was a member of the Masonic Lodge and a veteran of both World Wars. He is survived by his widow, a sister and a brother.

D. W. Heusinkveld, Governor for Ohio.

KENNETH L. BURT
1901 - 1950

Dr. Kenneth L. Burt died suddenly at his home in Kalamazoo, Michigan, July 2, 1950. He was born at Encampment, Wyoming. At the age of six he moved with his parents to Freemont, Michigan, where he attended the Freemont Elementary and High School, graduating in 1919. In 1923 he received a Bachelor of Science degree from Michigan State College. The following year he did research work in the Chemistry Department of the College and from 1925 to 1929 he was employed as a Chemist by Butterworth Hospital in Grand Rapids, Michigan. In September, 1929 he

entered the University of Chicago receiving his M.D. degree in 1935. While at the University, he took special training and did special work in research pathology. He was married to Miss Myrtle Pierce, May 2, 1931.

Following graduation from Medical School, he joined the staff of the Michigan State Sanatorium at Howell, Michigan, and immediately began research studies in tuberculosis. His work resulted in several published papers. In 1941 he moved to Erie, Pennsylvania, to become Chief Pathologist at St. Vincent's Hospital, a position he continued to hold until failing health made it necessary for him to retire in April 1949. He and Mrs. Burt later came to Kalamazoo hoping a prolonged period of rest and freedom from responsibility would be beneficial. Sudden death from acute myocardial infarction occurred July 2, 1950. Mrs. Burt is his only survivor.

He belonged to Sigma Alpha Epilson Social Fraternity and Nu Sigma Nu Medical Fraternity. In addition, he held memberships in the following societies: American Medical Association, American College of Chest Physicians, American Trudeau Society, American Society of Clinical Pathologists, American Bacteriologist Society, Kalamazoo Academy of Medicine, Michigan Pathological Society and Michigan State Medical Society.

Willard B. Howes, Governor for Michigan.

MICHAEL GLEASON
1901 - 1951

Dr. Michael Gleason was born in Thorville, Illinois, on January 19, 1901, and died in Mendota, Illinois, where he had practiced for several years and was actively interested in the affairs of his community.

Dr. Gleason, after completing his elementary education in Nebraska, received his Bachelor of Science degree in 1923 and his degree of Doctor of Medicine in 1927, from Creighton University. He was intern at Allied Hospitals Sisters of Charity, Buffalo, New York in 1928. Early in his medical life he became interested in Chest Diseases and served as Chest Consultant at Finney General Hospital, Thomasville, Georgia, followed by service as Major in the Medical Corps, U. S. Army, 1942-1946. Postgraduate training at Temple University School of Medicine under Dr. Chevalier Jackson further fitted him for his interest in Chest Disease and he served as Director of La Salle County Tuberculosis Sanatorium in 1947.

Dr. Gleason was vice-president of the staff of St. Mary's Hospital, La Salle, Illinois, and President of La Salle County Medical Society in 1949. He was a member of the Illinois Medical Society, American Medical Association and American Trudeau Society. For several years Dr. Gleason had participated as a Fellow in the activities of the American College of Chest Physicians.

Dr. Gleason died very suddenly on December 25 of coronary occlusion. Our departed Fellow is survived by his wife and two sons Michael J. and Malcolm P.

Those of us in the Illinois Chapter of the College share with his family the keen sense of loss which has come with the passing of Dr. Gleason. He was a fine physician, devoted to his family and actively interested in the welfare of his fellow men.

Charles K. Petter, Governor for Illinois.

THADDEUS M. KOPPA
1908 - 1950

Dr. Thaddeus M. Koppa was born December 10, 1908, in Illinois. He attended the University of Illinois at Urbana and graduated from the Medical School of the University of Illinois in 1932. He received the degree of Master of Public Health at the University of California in 1938. He was a member of his local, state and national medical societies. He was also a member of the American Public Health Association, the Michigan and American Trudeau Societies, and the American College of Chest Physicians. He taught medicine and epidemiology at different times at the University of Illinois, University of Michigan, Wayne University, and Michigan State College. At the time of his death he was Chief of the Tuberculosis Division, Branch 10, Veterans Administration.

He was the author of numerous articles in the field of tuberculosis and public health. He served on numerous committees in the field of tuberculosis and public health in the state of Michigan.

Through his ability as an organizer he established significant conferences for the benefit of chest specialists in the medical profession by means of which the standards of medical practice in tuberculosis control and care in the community, as well as in the sanatoria, have been raised. The conference held in Southwest Texas each year has been named the Thaddeus M. Koppa Conference in his honor.

Elliott Mendenhall, Governor for Texas.

JAMES LeROY ANDERSON
1886 - 1951

Dr. James LeRoy Anderson, San Antonio, Texas, died February 33, 1951, from coronary thrombosis.

Dr. Anderson was born September 17, 1886, in Ailsa Craig, Ontario, Canada, the son of James Ross and Katherine MacKay Anderson. He attended Park Hill High School, Park Hill, Canada, and was graduated from the Western University Faculty of Medicine, London, Ontario, in 1909, after which he interned at Pittsburgh Tuberculosis League Hospital. He was superintendent at Chicago Winfield Tuberculosis Sanatorium, Winfield, Illinois, from 1914 until 1918. Dr. Anderson practiced at Minot, North Dakota and served in the United States Army Medical Corps. He had been medical director of Grace Lutheran Sanatorium, San Antonio, since 1921. Dr. Anderson was a member of the American College of Chest Physicians and specialized in pulmonary diseases.

A member of the American Medical Association, he was a member of the State Medical Association through Bexar County Medical Society. He was a member of the Presbyterian Church.

Dr. Anderson is survived by his wife, the former Miss Clara Leland, whom he married in Chicago, October 12, 1915. He is also survived by a sister, Miss Belle Anderson, Toronto, Canada.

Elliott Mendenhall, Governor for Texas.

COLLEGE EVENTS

Semi-Annual Meeting, Board of Regents, American College of Chest Physicians, Los Angeles, California, December 2-3, 1951.

Southern Chapter Meeting, Dallas, Texas, November 4-5, 1951.

Chicago Postgraduate Course, September 24-28, 1951.

Minneapolis Postgraduate Course, October 18-20, 1951.

Portland Postgraduate Course (Oregon), October 29-31, 1951.

New York City Postgraduate Course, November 12-17, 1951.

MEDICAL SERVICE BUREAU

Positions Available

Research Fellow in Medicine, Tufts College Medical School and Resident in Medicine, Boston City Hospital, Dr. M. S. Segal's laboratory, available July 1, 1951 or January 1, 1952. Board, room and adequate salary for someone interested in diseases of the chest. Please write Dr. Maurice S. Segal, Director, Department of Inhalational Therapy, Boston City Hospital, Boston, Mass.

Position open for fellowship in diseases of the chest with emphasis on research on physiologic methods in the study and treatment of chronic nontuberculous and tuberculous pulmonary disease; also, participation in an investigation of cardiac failure. Fellowship allows sufficient clinical experience to count for National Boards. Salary, $3600. If candidate has completed three years for Boards, salary $4200 to $5000. Please write Dr. Alvan L. Barach, Presbyterian Hospital, 620 West 168th Street, New York, New York.

Applications accepted for staff and resident physicians, 235 bed, tuberculosis sanatorium 35 miles from New York City. Active teaching and research program. Part of large teaching hospital and approved for training in pulmonary diseases. Write to Director, Montefiore Hospital, New York 67, New York.

Resident physician wanted for 60 bed sanatorium, excellent facilities for medical and surgical treatment of chest diseases. Salary from $5000 to $6000, per year with full maintenance, depending upon experience. Graduate of American school with tuberculosis training preferred. Please address Box 224A, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Illinois.

Medical assistant needed at tuberculosis hospital in Ohio; graduate of American school, eligible for Ohio license. Salary open. Single man or woman preferred. Please address Box 225A, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Illinois.

Staff physician wanted for 160 bed tuberculosis hospital situated in the Pacific Northwest. Physician should be eligible for Oregon license. Salary $495 to $555 per month with complete maintenance. Full particulars given upon request. Please address inquiries to Box 221A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Resident for 175 bed, fully approved, tuberculosis hospital; salary $3000 per year, less nominal sum for maintenance. Please apply to Medical Director, Mahoning Tuberculosis Sanatorium, 4880 Kirk Road, Youngstown 7, Ohio.

Two thoracic surgeons offer attractive position to either a medical or surgical associate. Practice confined to diseases of the chest. Young, well-trained, middle-westerner or westerner preferred. Board qualification desirable. For further particulars please write Box 222A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Position Wanted

Thoracic surgeon, 36 years of age, with considerable experience in surgical treatment of tuberculosis, qualified for boards in thoracic and general surgery, now engaged in private practice, desires position doing thoracic surgery with or without general surgery. In draft classification IV. Will accept group, associate, or sanatorium position. Please write Box 251B, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Illinois.

NEWS

Dr. Charles E. Dutchess, Medical Director of Schenley Laboratories, has recently been elected a vice-president as well as a director of that company.

Paul W. Lyddon has been placed in charge of medical and dental x-ray product advertising for Eastman Kodak Company.

Dr. Harold J. Byrne has been appointed Director of Clinical Research at Commercial Solvents Corporation. He will be in charge of clinical evaluation of new drugs and antibiotics at the company's research center in Terre Haute, Indiana.

Armour and Company, Chicago, will shortly open a new plant in Buenos Aires, Argentina, to tap new sources of raw material to relieve a potential shortage of insulin and increase supplies of ACTH and trypsin.

Eli Lilly and Company has announced plans to establish a modern blood-processing unit. The new unit, to be set up and operated in Indianapolis for the Armed Services Medical Procurement Agency of the United States, will be completed late this year.

Dr. D. B. Keyes has resigned as vice-president of Heyden Chemical Corporation but will continue his association with that company in the capacity of a special consultant. Dr. Keyes is a Director of the company.

SANATORIUM DIRECTORY

The sanatoria listed in this section are among the finest sanatoria in the United States. They are prepared to offer private, individual, specialized care to your patients.

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For listings in the SANATORIUM DIRECTORY write to the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

ALUM ROCK SANATORIUM
San Jose, California

CALIFORNIA SANATORIUM
Belmont, California

CRAGMORE SANATORIUM
Colorado Springs, Colorado

EUDOWOOD SANATORIUM
Towson, Maryland

MARYKNOLL SANATORIUM
Monrovia, California

PALMER SANATORIUM
Springfield, Illinois

ROCKY GLEN SANATORIUM
McConnelsville, Ohio

SCHATZALP SANATORIUM DAVOS
Davos, Switzerland

ST. JOHNS SANITARIUM
Springfield, Illinois

SOUTHERN SIERRAS SANATORIUM
Banning, California

SOUTHWESTERN PRESBYTERIAN SANATORIUM
Albuquerque, New Mexico

THE SAMUEL AND NETTIE BOWNE HOSPITAL
Poughkeepsie, New York
Immobilizing Lung Chamber Therapy and Other Modern Methods of Treatment

SANATORIO ALBERTAL
Buenos Aires, Argentina

SANATORIO SAN ANGEL
Mexico City, Mexico

SWEDISH NATIONAL SANATORIUM
Englewood (Denver) Colorado
Modern Equipment — Moderate Prices

WORKMEN'S CIRCLE SANATORIUM
Liberty, New York

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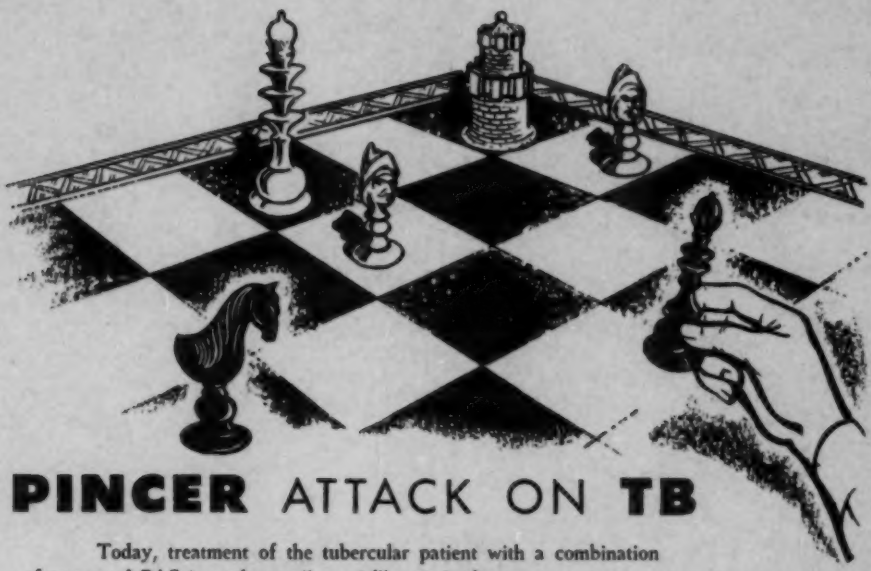

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*TEMPEL, C. W., FREDERIC, J. H. Jr., MARDIS, R. C., TOWBIN, M. N., and DYE, W. E. Combined intermittent regimens employing streptomycin and PAS, Am. Rev. Tuberc., 1951, 63, 295

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